PREDICTING PULMONARY HYPERTENSION AND OUTCOMES IN PATIENTS WITH LEFT HEART DISEASE

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DECLARATION

I, Anastase Innocent DZUDIE TAMDJA hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicated otherwise). I declare that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion.

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Date: ____August 10th, 2015_____

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Abstract

Background:

Pulmonary hypertension (PH) is defined as a rise in the pressure in the pulmonary arteries resulting from a variety of diseases including chronic infectious diseases, lung diseases and left heart diseases (LHD). It is a global health problem and accounts for a substantial portion of cardiovascular disease. PH due to LHD (PH-LHD) is credited to be the most common form of PH worldwide and is associated with adverse outcomes. Considering the suggestions of high prevalence and potential adverse outcomes of PH in sub-Saharan Africa (SSA), the investigation of the etiologies, clinical profile, correlates, and outcomes of PH-LHD in this region is a medical priority.

Methods:

Through a systematic review, we assessed existing evidence on the predictors of PH-LHD outcomes. Then, through two prospective multinational cohort registries, we investigated 1) the spectrum of PH in SSA; 2) the clinical profile and 6 months outcome of PH-LHD; 3) the role of electrocardiogram for diagnosing PH and 4) its prognostic role in heart failure (HF). PH was diagnosed by echocardiography in the context of clinical suspicion.

Results:

In high income countries, PH-LHD is almost invariably associated with increased mortality risk, but the effects on hospitalization are yet to be fully characterized. All groups of PH are found in SSA with LHD being the major cause. PH-LHD affects young people and is predominantly due to HF and rheumatic valvular heart disease. In these patients, left atrium size and tricuspid annular plan excursion are predictors of pulmonary pressures, and PH-LHD predicts short term hospitalization but not mortality. A normal electrocardiogram is very rare in patients with PH, but electrocardiogram criteria of right ventricular strain are rather rare and non-specific. Similarly, electrocardiogram abnormalities are frequent among Africans with HF, some have prognostic value for mortality risk.

Conclusion: PH-LHD is the most common form of PH in SSA, with affected patients presenting with advanced disease, and it is associated with adverse outcomes. ECG abnormalities are prevalent in both PH and HF, but few of these abnormalities have prognostic value for mortality risk. Evaluating the efficacy and safety of low-cost and available drugs in reducing HF hospitalizations in PH-LHD is a key future priority. Improving early diagnosis of PH should also be encouraged.

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Abbreviations used in the text

BMPR	Bone Morphogenic Protein Receptor
95% CI	95% Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DE	Doppler echocardiography
EF	Ejection fraction
FC	Functional class
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IVSd	Interventricular septal thickness at end-diastole
LHD	Left heart disease
LV	Left ventricular
LVIDd	Left ventricular internal dimensions at end-diastole
LVIDs	Left ventricular internal dimensions at end-systole
mPAP	Mean pulmonary artery pressure
NT Pro-BNP	N-Terminal pro Brain Natriuretic Peptide
OR	Odds ratio
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure

PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PH-LHD	Pulmonary hypertension owing to left heart disease
PVR	Pulmonary vascular resistance
PWd	Posterior wall thickness at end-diastole
RAE	Right atrial enlargement
RAP	Right atrial pressure
RV	Right ventricle
RVE	Right ventricular enlargement
RVH	Right ventricular hypertrophy
RVSP	Right ventricular systolic pressure
SPAP	Systolic pulmonary artery pressure
SSA	sub-Saharan Africa
TPG	Transpulmonary pressure gradient
WHO	World Health Organization

Preface

Summary of Chapters

Chapter 1 of this PhD thesis is an overview of the literature reviewing the current knowledge and concepts on the definition, diagnostic strategy of pulmonary hypertension (PH), prevalence and correlates of PH due to left heart disease (PH-LHD). In a published systematic review, we also investigate the predictors of hospitalizations for heart failure and mortality in patients with PH-LHD. The chapter ends with a description of the gaps in the knowledge that subsequent chapters will attempt to address.

Chapter 2 describes the hypothesis, aim and specific questions investigated in this doctoral research.

Chapter 3 is a description of the two major prospective multicentric cohort studies that form the basis of the analyses presented in this thesis, including the sub Saharan Africa survey of heart failure (THESUS-HF) and the Pan African pulmonary hypertension cohort (PAPUCO) study. This chapter also contains a second publication on the rationale and design of the PAPCUCO registry. In the PAPUCO registry, PH was diagnosed using Echocardiography, defined as a right ventricular systolic pressure (RVSP)>35 mmHg in the absence of pulmonary stenosis and acute right heart failure, and in a patient with clinical suspicion of the disease, with electrocardiogram (ECG) and chest x-ray changes in keeping with PH.

Chapter 4 to 7 present the results of this thesis in terms of condensed publications including notations as to if the manuscripts are still under review or, in terms of full publications, when they were accepted and published in peer-reviewed journals.

- In Chapter 4 (under review), we present the baseline characteristics, clinical profile, etiological types and outcome of patients with PH in sub Saharan Africa. PH generally affects women who are poorly or uneducated and exposed to indoor fumes, from cooking. All groups of PH are found in SSA with left heart disease being the dominant etiology. PH is associated with a high 6-month mortality rate and right heart failure is a predictor of death in these patients.

- Chapter 5 (under review) focuses on PH due to left heart disease (PH-LHD). We describe the clinical profile and predictors of PH-LHD, and the 6-month outcomes with their corresponding predictors. PH-LHD in our cohort was predominantly due to heart failure and its etiologies, and rheumatic valvular heart disease. Left atrium size and tricuspid annular plan excursion (TAPSE) were predictors of RVSP in patients with PH-LHD, and RVSP predicted short term hospitalizations, but not mortality.

- In Chapter 6 (under review), we investigated the diagnostic utility of electrocardiogram (ECG) in patients with PH. Our findings demonstrated that a normal ECG is very rare among patients with PH. Furthermore, most of these abnormalities are non-specific and ECG abnormalities relating to right heart strain are less frequent. ECG patterns focusing on the R and S amplitude have the best negative predictive values.

- Chapter 7 (full publication) investigated the predictive value of ECG for mortality risk in patients with heart failure. The study showed that ECG abnormalities are almost universal among Africans with acute heart failure, and some of these ECG findings have prognostic value for risk of death, but most of the abnormalities add little to the risk stratification.

Chapter 8 summarizes the major findings of this thesis and discusses the implications for recommendations regarding future research priorities on PH in low and middle income countries.

Appendix is a compendium of documents that were mandatory for the conduct of this doctoral research including the list of contributors to the two multinational cohort registries, the questionnaires and ethical approvals from various participating centers.

Author's contribution

The main studies that have contributed data to the analyses presented in this PhD thesis were multicenter and multinational collaborative studies, and therefore involved many investigators (list provided in the Appendix section). My specific role in relation to each of these studies is outlined below:

The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF)

I was the Cameroon investigator in this project from 2008 to 2014. I participated in all phases from the conception of the protocol to recruitments of patients, interpretation of results and drafting of all related manuscripts. For the publication forming part of this PhD Thesis, I was responsible for hypothesis generation, writing of the protocol, planning and guidance of the statistical analyses, interpretation of results, writing of the manuscript, submission to journals, coordinating the response to reviewer's comments, and proof reading the final copy.

The Pan African Pulmonary hypertension cohort study (PAPUCO)

I joined the PAPUCO team in 2012 and after protocol training, I succeeded in creating PAPUCO Cameroon's network of 03 local investigators. This included training the team, my involvement in patient recruitment activities and data entry on the web platform. I participated in the training of our local investigators on the research methodology and protocol implementation. I was a member of the data cleaning and management committee, co-conducted the statistical analysis and contributed to planning future directions. For the papers included in the PhD thesis, I participated in the hypothesis generation, I participated in all steps of data analysis, data interpretation, and drafting of manuscripts relating to the project.

Chapter 1. Background of the Thesis

1.1. Conceptual definition and historical perspectives on pulmonary hypertension

Pulmonary hypertension (PH) is an elevation of the pressure in the lungs' arteries, resulting from a variable combination of increases in pulmonary vascular resistance (PVR), pulmonary blood flow and pulmonary venous pressure (PVP) (1). This definition applies irrespective of the underlying etiology of PH which includes a range of conditions such as obstructive sleep apnea, lung diseases and left heart diseases. Pulmonary arterial hypertension (PAH), a specific type of PH, is a disease of the blood vessels of the lungs causing elevation in pressure. This section provides a historical perspective on PH.

Over the last century, significant progresses in the diagnosis and management of PH have gradually moved this condition from an orphan disease to a multidisciplinary and now acknowledged major global public health problem which affected more than 25 million individuals worldwide in 2010 (2, 3). The first clinical case reports on PH are attributed to the German physicians Klob in 1865 (4) and Romberg in 1891 (5) who both described a clinical-pathological syndrome characterized by the obstruction of the small pulmonary arteries and right ventricular hypertrophy in patients presenting with severe dyspnea and cyanosis. Nearly nine decades later, in the 1960s, several authors reported on an epidemic of PH cases in Europe due to appetite-suppressants (6-8). Almost concomitantly, with the development of right heart catheterization in the second half of the 20th century (9), it was found that many diseases could cause PH and the distinction between pre and post capillary PH was made. Nevertheless, it remains widely believed that PH is a rare fatal disease. Although true for idiopathic pulmonary arterial hypertension (PAH) or the formerly known primary PH, a condition which affects around six to ten individuals per million population in high income countries, the true burden of PH at large is currently unknown and largely underestimated (10). Interest has previously focused on studying the disease and this has led to increased recognition and development of new therapies. Pre-capillary PH now describes a group of

noninfectious, nonmalignant respiratory diseases causing breathlessness, loss of exercise capacity and leading, in the advanced form, to irreversible right heart failure (HF), a decreased quality of life and premature mortality (11). PH is largely recognized simply as high blood pressure in the pulmonary circulation.

Mitral valve stenosis due to rheumatic heart disease was the most common cause of PH before the 1950s (4, 12). However, this has greatly changed with the enormous and growing global burden of heart failure (HF) over the last 50 years. Left heart disease (LHD) in general (valvular heart disease or HF due to hypertension, ischemic heart disease, peripartum cardiomyopathy etc.) has progressively been credited to be the most common cause of PH in contemporary clinical settings (13, 14). Furthermore, among patients with LHD, some will develop a pre capillary component with pulmonary arterial disease, compounding the effects of the initial increase of pulmonary pressures(15). However, a great contrast still persist between the abundant literature on PAH and the paucity of data on PH due to LHD (PH-LHD). An operational definition better highlights the relevant distinction between PH at large and PAH and has been of major focus at all previous world meetings on PH. The next section is on the main operational definitions of PH.

1.2. Operational definitions of pulmonary hypertension

Pulmonary hypertension (PH) is currently defined as a pathological condition with an increase in mean pulmonary arterial pressure (PAP) beyond 25 mmHg at rest as assessed by right heart catheterization (16, 17). This hemodynamic definition of PH is not evidence-based. According to the 4th World Symposium on PH held in Dana Point in 2008 (18), a mean pulmonary artery pressure (mPAP) <21 mmHg was defined as normal, from 21 to 25 mmHg as borderline, and mPAP >25 mmHg was considered as overt PH. Correspondingly, echocardiographic systolic tricuspid regurgitant velocity thresholds <2.5 m/s were defined as normal, 2.5 to 2.8 m/s as borderline, and >2.8 m/s as highly suggestive of an overt PH. A more pragmatic definition by echocardiography uses right ventricular systolic pressure, commonly estimated from the velocity of tricuspid regurgitation. PH is then defined as an elevation of RVSP above 35 mmHg (19). Table 1 summarizes these definitions. As shown on Table 2, the 2015 joint European Society of Cardiology (ESC) – European Respiratory Society (ERS) further defines and

distinguishes pre- and post-capillary PH, Isolated post-capillary PH and combined post-capillary and pre-capillary PH using diastolic pressure gradient, mPAP and pulmonary arterial wedge pressure.

Table 1: Thresholds of pulmonary hypertension determined at the 4th World Symposium held in Dana Point 2008 (20).

Definitions of pulmonary hypertension		
Invasive (mean Pulmonary artery pressure)	Normal	< 21 mmHg
	Borderline	21 – 25 mmHg
	Manifest	>25 mmHg
Noninvasive (systolic tricuspid regurgitant velocity threshold)	Normal	<2.5 m/s
	Borderline	2.5 – 2.8 m/s
	Manifest	>2.8 m/s

Table 2: Operational (or hemodynamic) definitions of pulmonary hypertension according to European Society of Cardiology/European Respiratory Society (21)

Definitions	**Characteristics[a]**	**Typical clinical groups[b]**
PH	Mean PAP > 25 mmHg	All
Pre-capillary PH	Mean PAP > 25 mmHg Pulmonary wedge pressure ≤ 15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH (pc-PH)	Mean PAP > 25 mmHg PAP > 15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated pc-PH	DPG <7 mmHg and/or PVR ≤3 WU	
Combined post-capillary and pre-capillary PH	DPG≥7 mm Hg and/or PVR >3 WU[c]	

CO ¼ cardiac output; DPG ¼ diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP ¼ mean pulmonary arterial pressure; PAWP ¼ pulmonary arterial wedge pressure; PH ¼ pulmonary hypertension; PVR ¼ pulmonary vascular resistance; WU ¼ Wood units.

[a] All values measured at rest; [b] See also section 1.3.3. [c] Wood Units are preferred to dynes.s.cm^{-5}.

The term pulmonary arterial hypertension (PAH) defines a subpopulation of patients with PH hemodynamically characterized by the presence of pre-capillary PH comprising an end-expiratory pulmonary artery wedge pressure ≤ 15 mmHg and a pulmonary vascular resistance (PVR) >3 Woods units. As a subtype of PH, PAH is a group of diseases characterized by a progressive increase in PVR leading to right ventricular (RV) failure and death (23).

1.3. Diagnostic strategy and clinical classification of pulmonary hypertension

The diagnostic approach for a patient with suspected PH requires a clinical evaluation and a number of investigations to confirm the diagnosis and subsequent classification of the disease within the specific etiologic PH groups and deciding on the appropriate therapy. The diagnostic strategy for PH is summarised hereafter in four steps: 1) detection of a predisposing condition in which the likelihood of PH may be high; 2) uncovering of the presence of PH; 3) classification of the type of PH; and 4) confirmation of the presence of suspected PH.

1.3.1. Detection of a predisposing condition

A number of conditions summarized in Table 3 are recognized from a European perspective as predisposing factors to the development of PH. African data are lacking and may differ, we described
below three conditions that are relevant to sub-Saharan Africa (SSA).

1.3.1.1. Human immunodeficiency virus (HIV) infection

HIV-infected patients have a 2500-fold increased risk of developing PAH (22). Though the pathogenesis is yet to be fully understood, it has been postulated that during the course of HIV infection, secretion of inflammatory and immune response mediators such as endothelin-1 may contribute directly to endothelial damage (23).

1.3.1.2. Sickle cell disease

In sickle cell disease patients, persistent intravascular haemolysis for decades can lead to haemolysis-mediated endothelial dysfunction and chronic vasculopathy, with approximately 10% of patients developing PAH (24).

1.3.1.3. Schistosomiasis

In people infected with schistosomiasis, chronic infection in particular from Schistosoma mansoni, causes PH. The mechanisms seem to involve: parasite egg–induced pulmonary vascular granulomas; antigen or interleukin-13 associated vasculopathy and ensuing cascade; underlying liver disease and ensuing portal hypertension emulating portopulmonary hypertension pathophysiology; or a combination of these mechanisms (25, 26).

1.3.2. Uncovering the presence of PH

When PH is suspected, the patient shall undergo a clinical evaluation and a battery of investigations to confirm the diagnosis, clarify the clinical group of PH and the precise etiology within the PH group, and evaluate the functional and haemodynamic impairment.

1.3.2.1. Clinical evaluation

Pulmonary hypertension should be suspected in any patient with otherwise unexplained shortness of breath or fatigue upon exertion, dizziness, coughing and wheezing, cyanosis, syncope and/or signs of right ventricular dysfunction. At the early stages of the disease, the signs and symptoms of PH are subtle and may not be apparent for months or even years as well as generally non-specific (27-29).

Clinical examination may reveal the following (30): a left parasternal lift, an accentuated pulmonary component of second heart sound, a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, a right ventricular (RV) third sound, a jugular vein distension, hepatomegaly, peripheral oedema and ascites and cool extremities. Presence of some physical signs might suggest severe PH including an accentuated pulmonary component of S2 (audible at apex in over 90%), an early systolic click,

a midsystolic ejection murmur, a left parasternal lift, a right ventricular S4 and an increased jugular “a” wave. In Table 4, we summarize the most common signs on physical examination that are suggestive of possible underlying causes or associated PH.

When the clinical evaluation is suggestive of PH, the patient should initially undergo non-invasive investigations which should where possible include as initial tests a chest X-ray, electrocardiogram (ECG) and echocardiography. The utilization of other investigations will depend on both the results of the above initial tests and the clinical context.

Table 3: Approach to predisposing conditions of pulmonary hypertension (31)

Substrate	Further assessment	Rationale
BMPR2 mutation	Echocardiogram yearly; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	Early detection of PAH; 20% chance of developing PAH
1st degree relative of patient with BMPR2 mutation or within pedigree of 2 or more patients with a diagnosis of PAH	Genetic counselling and recommendation for BMPR2 genotyping; proceed as above if positive	Autosomal dominant transmission
Systemic sclerosis	Echocardiogram yearly; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	About 8% (by RHC) and 27% (by echocardiogram screening) prevalence of PAH in systemic sclerosis
Human immunodeficiency virus infection	Echocardiogram if symptoms or signs suggestive of PAH; RHC if echo demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	0.5% prevalence of PAH
Portal hypertension	Echocardiogram if OLT considered; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	4% prevalence of PAH in candidates for OLT; PAH is predictive of poor OLT outcome
Prior appetite suppressant use (fenfluramine)	Echocardiogram only if symptomatic	Incidence of PAH is approximately 0.005% if agent used > 3 months
Congenital heart disease with shunt	Echocardiogram and RHC at time of diagnosis; consider repair of defect if significant left to right shunt present	High probability of PAH developing in unrepaired shunt (Eisenmenger syndrome)
Recent acute pulmonary embolism	Ventilation-perfusion (V/Q) scintigraphy 3 months after event if symptomatic; pulmonary angiogram if positive	3% risk of chronic thromboembolic PH; negative VQ scan excludes chronic thromboembolism
Sickle cell disease	Echocardiogram yearly; RHC if echocardiogram demonstrates evidence of PAH (high right ventricular systolic pressure or right heart chamber enlargement)	30% develop PH, about 10% develop PAH, Increased mortality if PH present.
Schistosomiasis	-	10.7% to 18.5% prevalence in patients with hepatoesplenic schistosomiasis

BMPR2 indicates bone morphogenetic protein receptor 2; OLT, orthotopic liver transplantation; PAH, pulmonary arterial hypertension; and RHC, right heart catheterization

Table 4: Features of the Physical Examination suggesting underlying cause or associated pulmonary hypertension (32)

Physical Signs suggesting Possible Underlying Cause or Associations of pulmonary hypertension	
Central cyanosis	Abnormal V/Q, intra-pulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venopathy
Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Rales, dullness, or decreased breath sounds	Pulmonary congestion or effusion or both
Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic pulmonary hypertension
Splenomegaly, spider angiomata, palmary erythema, icterus, caput medusa, ascites	Portal hypertension

1.3.2.2. The role of electrocardiogram

Our knowledge of the contribution of ECG in the management of PH is limited and originates primarily from studies either on heart failure or pulmonary arterial hypertension. Guidelines from the European Society of Cardiology (33) and the National Institute for Clinical Excellence (34, 35) recommend that patients with suspected HF should have an ECG done in the diagnostic process. A normal ECG is very rare in the presence of heart disease. Of the 5934 patients who had an ECG done in the Euroheart survey (36), only 75 ECGs were normal. An abnormal ECG may show elements suggestive of heart disease and/or may provide more suggestive or supportive evidence for PH by demonstrating some signs that are common in patients with PAH. This include RV hypertrophy and strain, and right atrial dilatation as shown in Figure 1. The ECG has low sensitivity (55%) and specificity (70%) to be used as a screening tool for detecting significant PAH (37). ECG abnormalities have been associated with a short

survival in patients with primary PH (38), but the diagnostic and prognostic utility for other PH groups has yet to be explored.

1.3.2.3. Chest radiograph

The chest radiograph allows associated moderate-to-severe lung diseases to be reasonably excluded but also, abnormalities on chest radiograph are frequent in PH-LHD. Findings may reflect the underlying cardiac disease and include left heart or combined heart enlargement, left atrial enlargement, mild to moderate pleural effusion, cephalization or may reflect PH such as central pulmonary arterial dilatation, which contrasts with 'pruning' (loss) of the peripheral blood vessels (Figure 1). Right atrium and RV enlargement may be seen in more advanced cases. Overall, the degree of PH in any given patient does not correlate with the extent of radiographic abnormalities.

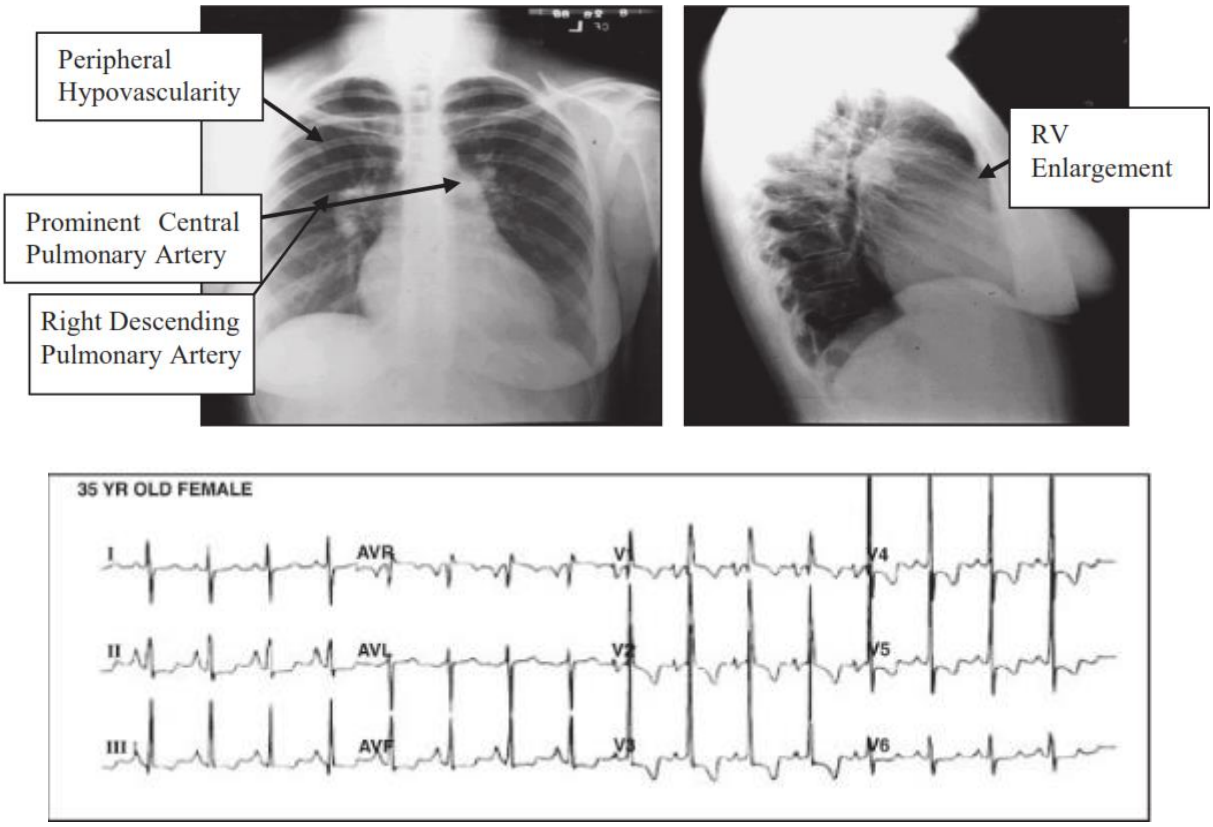

Figure 1: Chest X-ray and electrocardiogram in Pulmonary Arterial Hypertension (PAH)

A postero-anterior and lateral chest X-ray (upper panel) showing decreased peripheral lung vascular markings, hilar pulmonary artery prominence, and right ventricular enlargement of a patient with idiopathic PAH. An ECG (lower panel) of the same patient showing right atrial enlargement, right ventricular hypertrophy and strain, and right axis deviation of the QRS complex. Adapted with permission from McLaughlin et al (31).

1.3.2.4. The key role of transthoracic Doppler echocardiography

After a clinical evaluation of the patient with suspicion of PH, with or without presence of ECG or chest X-ray features, a transthoracic Doppler echocardiography (DE) examination is the next and most appropriate course of study. DE provides several variables which correlate with right heart hemodynamics including an estimate of RV systolic pressure (RVSP), and can simultaneously uncover functional and morphologic cardiac sequelae of PH, and assist in the identification of possible cardiac causes of PH.

1.3.2.4.1. Estimation of right ventricular systolic pressure and function

As shown in Figure 2, the Doppler echocardiographic (DE) estimation of PAP is based on the peak velocity of the jet of tricuspid regurgitation (TR). TR velocity can be obtained by either a duplex imaging from the right ventricular inflow view, parasternal short axis view at the basal level, para-apical four chamber view, apical four chamber view, or even the subcostal view. The TR maximal instantaneous gradient (TR MIG) is frequently automatically calculated and displayed on the screen (Figure 2) when the maximal TR velocity is measured. Else, it is easily calculated using the simplified Bernoulli equation (39): **TR MIG = 4(TR velocity) ^{2}.** The Bernoulli's equation then allows for the estimation of the right ventricular systolic pressure (RVSP) (39) taking into account right atrial pressure (RAP): **RVSP = TR MIG + RAP.** In this equation, RAP stands for right atrial pressure and is estimated as explained in Table 5.

Table 5: Estimation of right arterial pressure using the diameter of the inferior vena cava (39, 40)

Estimated right arterial pressure (mmHg)	Inferior vena cava diameter (cm)	Inferior vena cava collapse with inspiration (sniff)
0-5	<2.1	>50%
5-10	<2.1	<50%
10-20	≥2.1	<50%

In patients with PH, DE also contributes in the evaluation of the RV systolic function through measurement of the tricuspid annular plan systolic excursion movement (TAPSE). TAPSE represents the distance of systolic excursion of the RV annular plane towards the apex. As shown in Figure 2, it is obtained using an M-mode cursor passed through the tricuspid lateral annulus in a four-chamber view and measuring the amount of longitudinal displacement of the annulus at peak-systole. While it is an easy and simple parameter to use in patients with PH, it is necessary to emphasise that TAPSE measurement is an angle dependent parameter and it is influenced by LV function and overall heart motion.

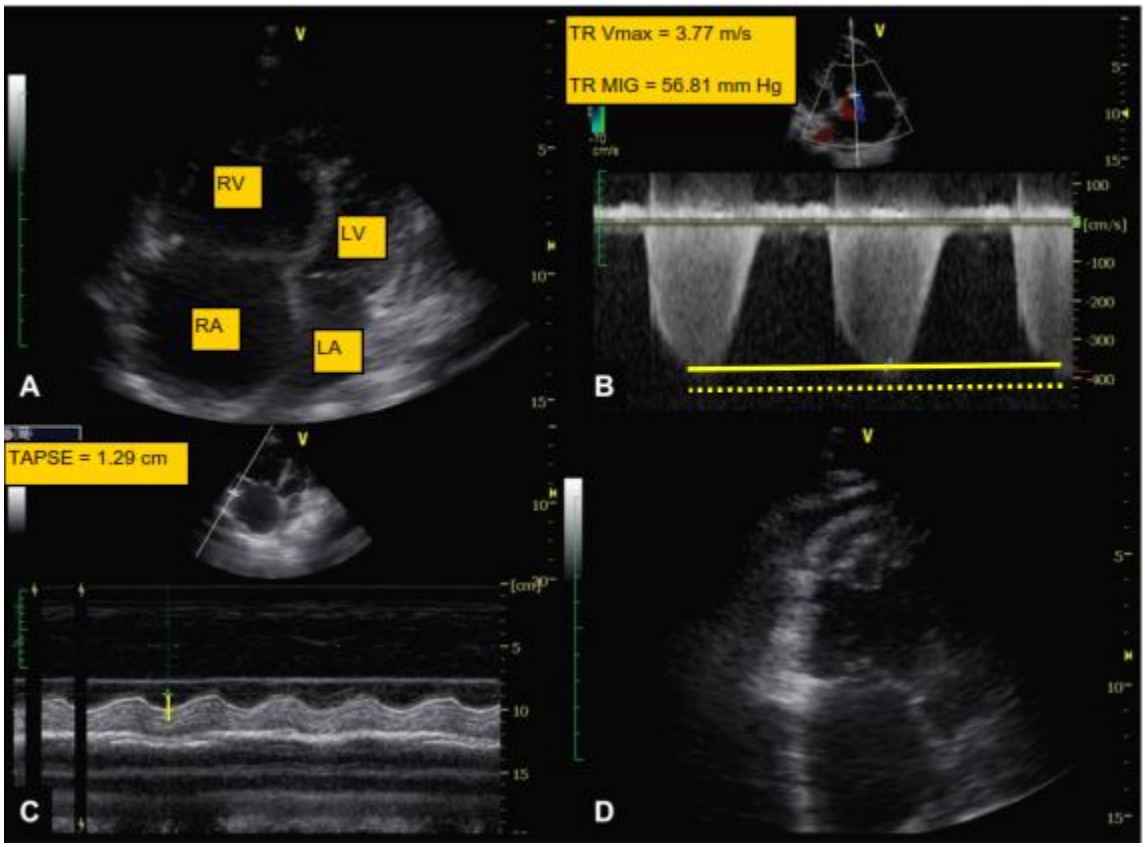

Figure 2: Diagnosing pulmonary hypertension using transthoracic two-dimensional Doppler echocardiography

(A) Four-chamber view showing grossly enlarged right ventricle (RV) and right atrium (RA); with right ventricularisation of the left ventricle (LV), and bulging of the RA into the left atrium (LA); (B) Color-wave and continuous-wave Doppler across the tricuspid valve in the four-chamber view showing severe tricuspid regurgitation (TR), despite the deceivingly less impressive color-flow jet seen across the valve; TR maximal velocity (TR Vmax) is indicated by the yellow solid line, the yellow dotted line indicates an over gained which can lead to an overestimation of the TR Vmax; (C) M-mode measurement of tricuspid annular plan excursion (TAPSE) depicting right ventricular systolic dysfunction; (D) Long-axis view of right ventricular apical thrombus. TR MIG, TR maximal instantaneous gradient. Adapted and modified from Thienneman F, Dzudie A, Mocumbi AO et al (41).

Right atrial pressure (RAP) is estimated based on the measured diameter and respiratory variation of the inferior vena cava (IVC) with the patient lying supine and the IVC brought into view in the long axis (Figure 3). RAP is then estimated as indicated in Table 5 above.

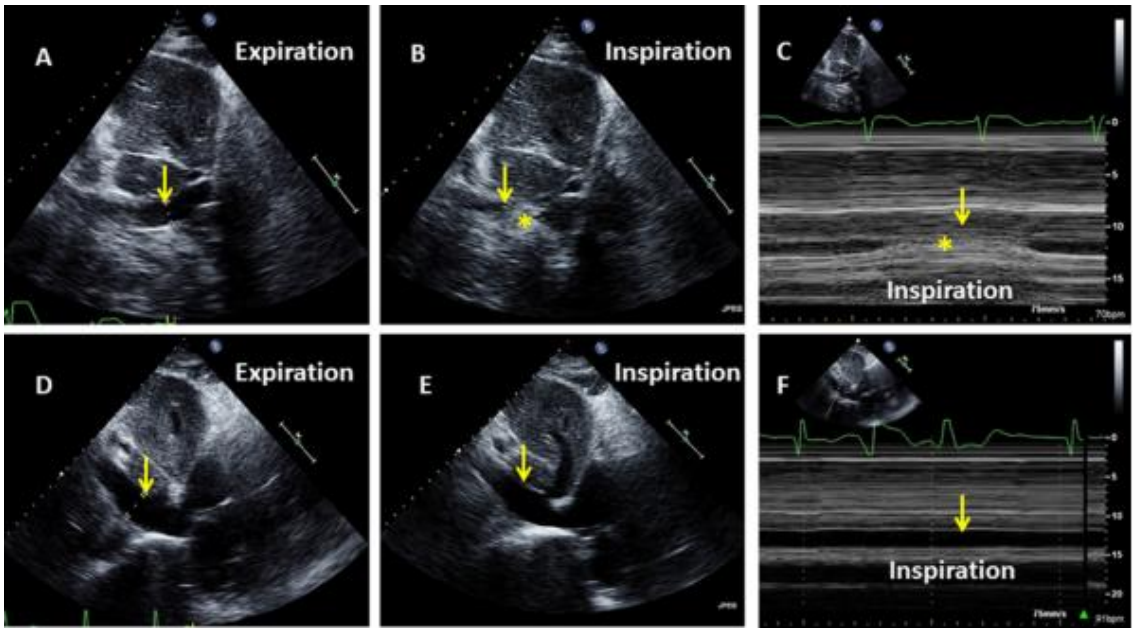

Figure 3: Echocardiographic evaluation of RAP using IVC dimension and collapsibility.

Subcostal 2DE during expiration (A) and inspiration (B) and M-mode echocardiography (C) demonstrating good inspiratory collapse (asterisk) of the inferior vena cava (IVC) (arrow) in a patient with normal RAP and 2DE during expiration (D) and inspiration (E) and M-mode echocardiography (F) demonstrating no inspiratory collapse of the IVC in a patient with elevated right atrial pressure. Adapted (with permission) from Beigel et al (40).

In the absence of pulmonary stenosis, the estimated RVSP is assumed to equal the pulmonary artery systolic pressure. To avoid errors in the measurement of RVSP, it is mandatory to observe the following conditions:

1) Measurement of the IVC diameter should be made just proximal to the junction of the hepatic veins that lies approximately 0.5-3.0 cm proximal to the ostium of the right atrium.
2) Avoid measuring over-gained (shaggy) signals (see the doted horizontal line in Figure 2 above) which results in an overestimation of the RVSP. The correct maximal TR velocity shall be measured in the shaggy, very faint portion of the Doppler signal as

indicated by the dense, sharply outlined Doppler signal. The horizontal line on this image indicates the true maximal TR velocity.

3) If the heart rhythm is irregular, it is recommended that 3-5 consecutive cycles be measured and the mean of these cycles be recorded.
4) The maximal TR velocity may be misleadingly low when severe TR is present due to severely increased RAP. In this case, other parameters must be used to assess whether or not pulmonary hypertension is present.

An estimated RV systolic pressure greater than 35 mmHg generally warrants further evaluation in a patient with unexplained dyspnea (19). Furthermore, other echocardiographic findings as an estimated RA or RV enlargement or intraventricular septal flattening, may also motivate further evaluation.

1.3.2.4.2. Echocardiographic functional and morphologic cardiac sequelae of pulmonary hypertension

Other echocardiographic findings that are consistent with PH include RA or RV enlargement (Figure 2) or RV systolic dysfunction as assessed by measuring a tricuspid annular plan excursion (TAPSE) (42). Furthermore, DE can also identify coexistent abnormalities which are not causally linked to PAH but are pathognomonic of the condition (Table 6).

Table 6: Possible causes of pulmonary hypertension identified by Echocardiography [(adapted from McLaughlin et al (32)]

Predisposing conditions to Pulmonary Hypertension
• Valvular disease (Mitral (Aortic) stenosis/regurgitation, prosthetic valve dysfunction) • Left ventricular systolic dysfunction (including hypertensive heart failure, dilated cardiomyopathy, peripartum cardiomyopathy, myocardial infarction etc.) • Left ventricular diastolic function (including ischemic heart disease, hypertensive heart disease, hypertrophic cardiomyopathy, Fabry's disease, infiltrative cardiomyopathies) • Other obstructive lesions (coarctation, supravalvular Aortic stenosis, subaortic membrane, cor triatriatum) • Congenital disease with shunt (Atrial (ventricular) septal defect, coronary fistula, patent ductus) arteriosus, anomalous pulmonary venous return) • Pulmonary embolus (thrombus in inferior vena cava, right-sided cardiac chamber, or pulmonary artery; tricuspid or pulmonic valve vegetation) • Pulmonary vein thrombosis/stenosis
Findings That Suggest Specific Disease Entity
• Left-sided valve changes (Systemic lupus erythematous, anorexigen use) • Intra-pulmonary shunts (hereditary hemorrhagic telangiectasia) • Pericardial effusion (Idiopathic pulmonary arterial hypertension, Systemic lupus erythematous, systemic sclerosis)

1.3.2.5. The role of other tests

A range of other tests can contribute to establishing a diagnosis of PH (30). These include:

- The 6-minute walk test (6MWT) which has been reported to have both a diagnostic and prognostic value in patients with PAH (38, 43, 44).
- A transoesophagal echocardiography might be necessary to better study congenital or acquired valvular heart disease.
- Arterial blood gases, cardiopulmonary exercise test, pulmonary function tests and computerized tomography of the chest which can show abnormal findings suggestive of a chronic obstructive pulmonary disease as a cause of PH.
- Ventilation-perfusion scintigram and/or pulmonary angiogram which can show arguments in favour of chronic thromboembolic PH (CETPH). A normal or very low probability essentially excludes CTEPH, and a high probability scan warrants further evaluation with a pulmonary angiogram.
- Antinuclear antibody serology, rheumatoid factor, C-reactive protein which patient should undergo if suspicion of connective tissue disease is warranted.
- The human immunodeficiency virus screening in case HIV infection is suspected as a contributing etiology of PH.

Once a definitive diagnosis of PH and been reached and potential underlying comorbidities or causes identified, classification in an appropriate etiologic group must be considered before discussing appropriate treatment. The paragraph below summarises the historical aspects of the clinical classification and describes the most current classification.

1.3.3. Classification of the type of Pulmonary Hypertension

With the first descriptions of the epidemic of drug induced PH caused by appetite suppressants in the 1960's (45, 46), a systematic collection of data on PH was initiated. This led to the first international classification conference on PH, endorsed by the World Health Organization in 1973 (47, 48). Since 1973, the clinical classification of PH has undergone a series of changes. The Evian classification was proposed in 1998 (49). This classification was based on similar pathophysiological mechanism, clinical presentation and therapeutic options, and was modified further in Venice in 2003 (50), where two relevant changes occurred. Firstly, the term idiopathic PAH (IPAH) was replaced by the term primary pulmonary hypertension (51). Secondly, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) were merged into a single subcategory of PAH. During the

fourth World Symposium on PH held in 2008 in Dana Point, California (20), consensus was achieved to maintain the general philosophy and organization of the Evian-Venice classifications and to amend some specific points that would improve clarity and take into account new information. The most updated clinical classification which derives from the 5th world symposium on pulmonary hypertension held in Nice in 2013 (Table 7).

With regard to the pathophysiology of elevated pulmonary artery pressures as well as to therapeutic concepts, PH-LHD has been further sub-classified according to the suspected underlying etiology (52), with a particular interest to provide a detailed differentiation between heart failure with reduced left ventricular ejection fraction (HFrEF; “systolic heart failure”), heart failure with preserved ejection fraction (HFpEF; “diastolic heart failure”), left-sided valvular heart disease, and other causes (52).

Table 7: Updated clinical classification of pulmonary hypertension from the 5th World Symposium on Pulmonary hypertension, Nice 2013 (18, 53).

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic pulmonary arterial hypertension
1.2. Heritable pulmonary arterial hypertension
1.2.1. Bone Morphogenetic Protein Receptor 2
1.2.2. Activin receptor-like kinase-1, Endoglin, Mothers against decapentaplegic homolog 9, Caveolin-1, Potassium channel subfamily K member 3
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. human immunodeficiency virus Infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1" Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
2.4. 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Table 8: Classification of pulmonary hypertension due to left heart diseases (52)

Heart failure with reduced ejection fraction (HFrEF; EF ≤50%)*	
• Ischemic cardiomyopathy • Dilated cardiomyopathy (Hypertensive heart failure, Peripartum cardiomyopathy, etc.)	
Heart failure with preserved ejection fraction (HFpEF; EF >50%)*	
• Hypertensive heart disease • Coronary heart disease • Diabetic cardiomyopathy	• Hypertrophic cardiomyopathy • Restrictive cardiomyopathy • Constrictive pericarditis
Valvular diseases	
• Aortic valve stenosis • Aortic valve insufficiency • Mitral valve stenosis	• Mitral valve insufficiency • Persistent/residual pulmonary hypertension after corrected valvular defect
Other causes	
• Atrial fibrillation • Other arrhythmias	• Triatrial heart • Myxoma or left atrial thrombus

*Instead of differentiating between systolic and diastolic heart failure, the differentiation between heart failure with reduced versus preserved left ventricular (LV) function (ejection fraction) is made in accordance with current recommendations and guidelines (54); in most cases, heart failure with reduced LV function is associated with signs of left ventricular diastolic dysfunction.

Because PAH, and particularly IPAH, is a diagnosis of exclusion, an algorithm is very useful as a starting point in any case of suspected PH. A diagnostic algorithm adapted to resource-constrained settings has been proposed in Chapter 3 of this thesis, on Page 129.

Finally, although the non-invasive estimation of RVSP, introduced to echocardiography laboratories in the 1990s by Stephen et al (55) is regarded with great excitement, an invasive test is still in principle warranted to confirm the diagnosis. In the next section, we discuss the relevance of right heart catheterization (RHC).

1.3.4. Confirmation of the presence of pulmonary hypertension

Cardiac catheterization is the standard test to definitively confirm any form of PH, define the hemodynamic profile with accuracy and determine prognosis and response to therapy.

Using RHC, PH has been defined as an increase in mean pulmonary arterial pressure (PAP) equal or above 25 mmHg at rest (53, 56). Available studies have shown that the normal mean PAP at rest is 14 ± 3 mmHg, with an upper limit of normal of being 20 mmHg (57, 58). This value has been used for selecting patients in most randomized control trials and registries of PH. The significance of a mean PAP between 21 and 24 mmHg is unclear (17). By directly measuring pressures and indirectly measuring flow, RHC allows the acquisition of prognostic markers such as RAP, cardiac output, and mean PAP. Other essential components of invasive hemodynamic assessment include oxygen saturations, RV pressure, systolic and diastolic PAP, pulmonary capillary wedge pressure, LA pressure or LV end-diastolic pressure, pulmonary vascular resistance (PVR), systemic BP, heart rate and response to acute vasodilator.

1.3.5. Echocardiography versus right heart catheterization in the diagnosis of pulmonary hypertension

While echocardiography has the advantage of being non-invasive and a useful screening tool for the presence of PH hypertension as described in section 1.3.1.3, it provides only an estimate of RVSP. Thus, confirming PH diagnosis with RHC before any specific therapeutic action is required. The inability of echocardiography to measure pulmonary capillary wedge pressure also argues for the relevance of RHC. However, RHC needs to be performed in specialized centers, remains an invasive procedure and as reported by Hoeper et al (59), even in expert's hands, has a non-negligible procedure-related mortality and serious events risk.

1.4. The burden of pulmonary hypertension in left heart diseases

The global epidemiology of PH as a whole is currently unknown, but is estimated to vary across regions of the world, socioeconomic and health system related factors. Nevertheless, there is a general consensus that LHD is the most common etiology worldwide. This section

is on the incidence, prevalence and determinants of PH-LHD as well as outcome and determinants of outcome of patients with PH-LHD.

1.4.1. Incidence of pulmonary hypertension in left heart disease

Incidence data on PH as a whole is scanty and available incidence studies have focussed on very specific groups. In people with systemic sclerosis, Foocharoen et al (27) have reported an incidence rate of 0.2 per 100 person-years in Thailand, while Yan et al (54) have found an incidence of 23.5% from 2004 to 2011 in patients with pulmonary fibrosis in China. The INCIPIT trial (INCidence of Pulmonary Hypertension in Italian ulTrasonography laboratories) is likely the only incidence study of PH as a whole and PH-LHD in particular (60). This study on 21,483 echocardiograms from 110 Italian centers showed that 1410 (6.6%) exams had a systolic regurgitant flow velocity $\geq$3 m/s (median value 3.3). The ratio of women/men among patients was 734/67. Their mean age was 71.8 years and median body mass index was 25.7 kg/m^2. Overall, 52.6% had left heart disease, 7.5% lung disease, 1.3% chronic thromboembolic pulmonary hypertension, while 26.4% had more than one comorbidities, and 10.5% had unknown etiology.

1.4.2. Prevalence and determinants of pulmonary hypertension due to left heart disease

Comparable prevalence data on different groups of PH are not lacking. In the Armadale echocardiography cohort (61), the prevalence of PH (defined as RVSP>40 mmHg) among 4579 patients was 10.5%. Among 936 cases with PH, 636 (67.9%) had PH-LHD, 87 (9.3%) had lung disease and hypoxia (group 3), 25(2.7%) had PAH (group 1), 19(2.2%) had chronic thromboembolic PH (group 4), 25(2.7%) were in PH group 5 and in 144(15.3%) patients, it was not possible to define a diagnosis.

Pulmonary hypertension occurs commonly in patients with LHD, with a high level of variability in its development and severity, and consequently a variability in prevalence due to the following reasons: 1) available data are largely derived from heart failure referral centers of different health care systems, very few from community-based HF populations (61, 62); 2) the diagnostic method and the criteria vary across studies; 3) populations have been

heterogeneous, in terms of symptoms, age, and the severity of the LHD; 4) the degree of hemodynamic decompensation at the time of echo or RHC assessment influences pressure measurement. In the following lines, we discuss and distinguish the prevalence of PH-LHD according its etiology (HF or valvular heart disease).

1.4.2.1. Prevalence and determinants of pulmonary hypertension in people with heart failure

The prevalence of PH-LHD in people with HF ranges from 19% to 83.3% and depends on the method and criterion used to define PH as well as the type of HF (Figure 4).

1.4.2.1.1. PH in heart failure with reduced ejection fraction

The prevalence of PH in HFrEF varies from 25 to 83.3%. In a tertiary care center of Pennsylvania, Abramson et al (63) studied 108 consecutive patients with HFrEF due to dilated cardiomyopathy, and reported the lowest echocardiographic prevalence of PH-LHD (25.9%) when PH was defined as a tricuspid regurgitation (TR) jet >2.5 m/s (Table 9). A contrario, in a retrospective population-based study in Tayside, Scotland, Szwejkowski et al (64) investigated 1612 patients with HFrEF and reported that PH (defined as RSVP>33 mmHg) was present in up to 83.3% of patients. Variable prevalence has been reported elsewhere (Figure 4).

1.4.2.1.2. PH in heart failure with preserved ejection fraction

Unlike PH in patient with HFrEF, PH in patients with HFpEF has been less documented; although there has been recent increasing awareness of the condition (Figure 4 and Table 9). In a study on the prognostic value of PH in hospitalized patients with HFpEF, Carrasco-Sanchez et al (65) reported a prevalence of 32.2% when PH was defined as a RVSP > 35 mmHg on DE. Using the same tool and the same definition, Lam et al (66) reported the highest prevalence of 83% in a community-based study of 244 HFpEF patients (Table 9). Another DE study by Damy et al in France (67) reported a prevalence of 46% with a definition of PH as a tricuspid gradient > 25 mmHg. In a retrospective review of 239 Lebanese patients with HFpEF who underwent right-side and left-side cardiac catheterization with ventriculography from

October 1996 to September 2007, 52.5% had PH, defined as mean pulmonary artery pressure >25 mmHg (68).

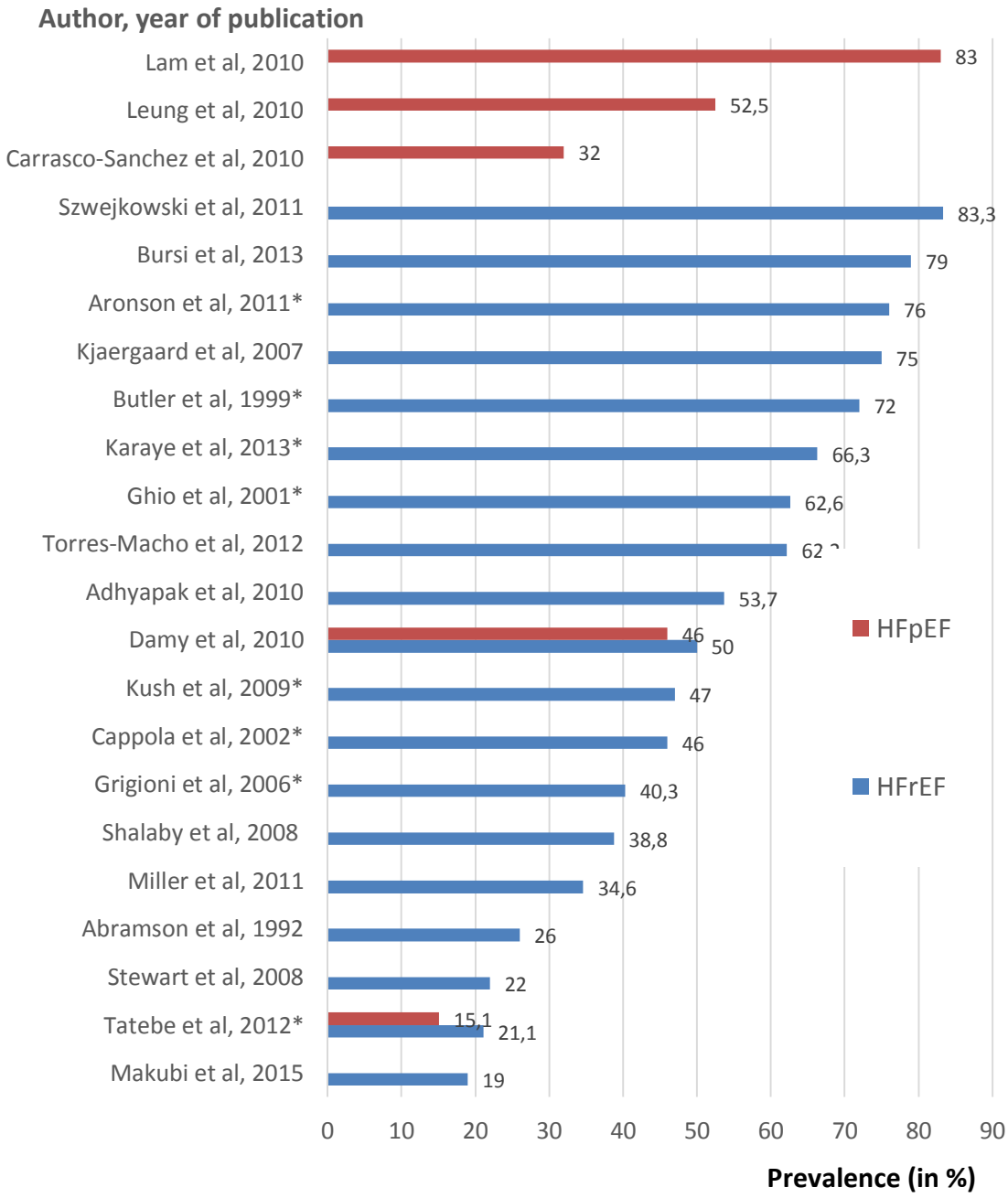

Figure 4: Variability of the prevalence of pulmonary hypertension in patients with heart failure

HFp(r)EF, Heart failure with preserved (reduced) ejection fraction. * Studies that used RHC for definition of PH.

Table 9: Prevalence of pulmonary hypertension in patients with heart failure [(adapted from Georgiopoulou et al (13)]

Study	N	Population	Method	Definition	Prevalence
Heart failure with predominantly reduced ejection fraction (Chronic)					
Stewart et al, 2008(69)	844	De novo cases of HF, mean LVEF=45%, 23% HFpEF	DE	RVSP>35 mm Hg	22%
Makubi et al, 2015 (70)		Prevalent cases of HF, mean LVEF=41%, 68% with HFrEF	DE	RVSP>35 mm Hg	19%
Torres-Macho et al, 2012(71)	419	Advance HF and left ventricular systolic dysfunction	RHC	mPAP>25 mmHg	62.2%
Abramson et al 1992 (63)	108	Dilated cardiomyopathy; mean LVEF 17.2%	DE	TR jet velocity >2.5 m/s	25.9%
Butler et al 1999 (72)	320	Ambulatory patients for therapeutic evaluation; LVEF 23±9%	RHC	PVR >1.5 WU	72%
Ghio et al, 2001 (73)	377	Ambulatory patients for treatment evaluation; LVEF 21.8±6.7%	RHC	mPAP>20 mmHg	63.2%
Cappola et al, 2002 (74)	1134	New-onset cardiomyopathy; LVEF: N/A		PAP ≥25 mmHg	46%
Grigioni et al, 2006 (75)	196	NYHA class III-IV; LVEF 27±9%	RHC	mPAP>25 mmHg	40.3%
Shalaby et al, 2008 (76)	270	Cardiac resynchronization therapy recipients; LVEF 22.6±9.7%	DE	RSVP>45 mmHg	34.8%
Adhypak et al, 2010 (77)	147	Ambulatory patients	DE	RSVP>45 mmHg	53.7%
Miller et al, 2011 (78)	1541	HF with LVEF ≤40%; LVEF 30.5±8.3%	DE	RSVP>45 mmHg	34.6%
Karaye et al, 2013 (79)	80	HF with LVEF 39.4±19.4 in PH vs. LVEF 48.5±19.8% in non PH group	DE	mPAP>25 mmHg	66.5%

Szwejkowski et al, 2012 (64)	1612	LVSD (qualitative), loop diuretics, and measured RVSP	DE	RVSP ≥35 mmHg*	83.5%
Bursi 2012 (62)	1049	Community inpatients and outpatients with HF, mean EF=47.6%	DE	RVSP >35 mmHg	79%
Heart failure with reduced ejection fraction (Acute decompensation)					
Kjaergaard et al, 2007 (80)	388	Admitted for acute HF; LVEF 33 (23–50)%	DE	RVSP ≥39 mmHg	50%
Khush et al, 2009 (81)	171	Acute HF, clinical trial; SBP ≤125 mmHg; LVEF ≤30%	RHC	Mixed PH: mPAP ≥25 mmHg; PCWP >15 mm Hg; PVR ≥3 WU	47%
Aronson et al, 2011 (82)	242	Acute HF, clinical trial; LVEF 25±13%	RHC	mPAP >25 mmHg	76.0%
Heart failure with preserved ejection fraction					
Lam et al, 2009(83)	244	Community inpatients and outpatients; LVEF ≥50%	DE	RVSP >35 mmHg	83%
Leung et al, 2010(68)	455	Cardiac catheterization registry; LVEDP >15 mmHg; LVEF ≥50%	RHC	mPAP >25 mmHg	52.5%
Heart failure with mixed populations (reduced or preserved ejection fraction, prevalence of HFrEF vs HFpEF)					
Tatebe 2011(84)	676	HF patients NYHA II-IV referred for RHC	RHC	mPAP ≥25 mmHg	21.1 vs 15.1%
Damy et al, 2010(67)	270	HFrEF (LVEF ≤45%) vs HFpEF (LVEF>45%), measured RVSP	DE	TR gradient >25 mmHg	50% vs 46%

DE, Doppler echocardiography; EF, ejection fraction; HF, heart failure; HFr(p)EF, HF with reduced(preserved) ejection fraction, LVEF; left ventricular EF, PAP, pulmonary artery pressure; mPAP, mean PAP; PASP, pulmonary artery systolic pressure, PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SBP, systolic blood pressure; RVSP, right ventricular systolic pressure. * No a priori definition of PH.

1.4.2.1.3. Cardiac structural and functional correlates of PH in patients with heart failure

In normal subjects, pulmonary artery pressure is correlated with age and BMI (85). In patients with LHD, the degree of PH is thought to be independently related to a certain number of factors among which the LV filling pressure, mitral regurgitation and RV dysfunction, regardless of LV systolic function or HF stage.

1.4.2.1.4. The role of left ventricular filling pressure and mitral regurgitation

Elevated left-sided filling pressure and functional mitral regurgitation are the two major determinants of PH in LHD. In the initial stage of all HF, an elevation of the LV filling pressure will consequently via a backward hemodynamic effect lead to an increase in LA pressure and LA dilatation. Functional mitral regurgitation (MR) occurring with LV systolic dysfunction inevitably leads to increasing LA pressure. In any case, increase LA pressure then causes an increase in hydrostatic pressure in pulmonary capillaries and the PH. In 102 consecutive patients with primary LV systolic dysfunction, Enriquez-Sarano et al (49), demonstrated that the development of PH in patients with systolic HF was strongly associated with restrictive LV filling pattern, a marker of increased chamber stiffness. In this study, ejection fraction and end-systolic volume were not independent predictors of pulmonary artery pressure. Other surrogates of elevated left ventricular filling pressures have also been found to be correlated with RVSP including LA volume (86).

1.4.2.1.5. The RV systolic function

RV systolic function is directly affected by increased SPAP, and the severity of RV systolic dysfunction strongly parallels progression of LV failure in patients with severe systolic HF(13). Studies have shown that RV function assessed using TAPSE, is impaired in HF, even when accounting for the degree of pulmonary hypertension, and that LV diastolic dysfunction and severe tricuspid regurgitation further aggravate RV dysfunction (87).

1.4.2.2. Prevalence and determinants of pulmonary hypertension in patients with valvular heart disease

Table 10 depicts the prevalence of PH from selected studies of patients with valvular heart disease. Mitral valve disease has been the classical cardiac disease associated with PH (4) and the presence of PH plays an important role in the evolution of the primary disease (88). Moderate to severe mitral stenosis (MS) is frequently associated with PH and the prevalence of PH itself likely vary according to the severity of the disease. In 559 patients with MS undergoing MBV, Fawzy et al (89) reported that the prevalence of mild PH in patients with severe MS was 62%, while the moderate PH was encountered in 33% and the severe PH in 5% of the study population. Hart et al (90) reported that up to 73% of patients with MS undergoing percutaneous balloon valvuloplasty have PH. Chronic isolated mitral regurgitation with preserved LV function is also frequently associated with PH. When the presence of PH is defined as sPAP>40 mmHg by RHC or RVSP>40 mmHg by echo, a prevalence of 53% was observed by Ghoreishi et al (91). In patients with degenerative MR, if the definition of RVSP>50 mmHg by echo was used, a prevalence of 23% was observed by Barbieri et al (92), whereas with a definition of sPAP≥50 mmHg, Magne et al described only 15% prevalence (93). A recent study of patients with asymptomatic MR showed that exercise-induced PH (sPAP>60 mmHg) was more common, with a prevalence of more than 46% compared with 15% prevalence of PH at rest (sPAP>50 mmHg) (93). This explains symptom development during exercise.

Aortic stenosis results in PH by inducing LV hypertrophy and subsequent LV diastolic dysfunction, which in turn leads to increased pulmonary pressures. Over time, structural changes in the pulmonary vasculature occur and PH might become irreversible. Compared with mitral stenosis, the prevalence of PH in patients with aortic stenosis tends to be lower, with a prevalence of approximately 30% (94). Although less frequently, aortic regurgitation (AR) can also lead to PH. The underlying mechanism is also chronic elevation of LVEDP, which in turn leads to an increase in left atrial and pulmonary artery pressures. Khandhar et al reported 16% of their patients with severe AR had severe PH (95).

In conclusion, mirroring patients with HF, an elevation in LV filling pressure and the occurrence of mitral regurgitation plays a major role in the development and severity of PH

in patients with LHD. How PH independently affects hospitalizations or mortality from heart failure as well as the potential predictors for these outcomes are discussed in the next paragraph.

Table 10: Prevalence of pulmonary hypertension from selected studies of patients with valvular heart disease

Study	N	Population	Method	Definition	Prevalence
Zühlke et al	3343	All rheumatic valvular heart disease	DE	RVSP>35 mm Hg	28.8%
Ward and Ward (96)	586	Mitral valve disease	RHC	SPAP > 80 mmHg and PVR>10 Wu	8.2%
Hart et al (90)	317	Mitral stenosis undergoing percutaneous balloon valvuloplasty	RHC	mPAP>25 mmHg TPG>15 mmHg	73% 19%
Magne et a l(93)	78	MR; severe in 60% of the cohort	RHC	Rest SPAP>50 mmHg	15%
Barbieri et al (92)	437	MR	DE	RSVP>50 mmHg	23%
Nozohor et al (97)	270	MR undergoing mitral valve surgery	DE	RSVP>50 mmHg	27%
Ghoreishi et al(91)	873	MR undergoing mitral valve surgery	RHC and DE	sPAP or RSVP mmHg>40 mmHg	53%
Johnson et al (98)	92	Severe AS	RHC	SPAP 31 – 50 mmHg SPAP>50 mmHg	34% 16%
Ben-Dor et al (99)	509	AS	DE	RSVP>30 mmHg	68.3
Silver et al (94)	45	Severe AS	RHC	SPAP>50 mmHg	29%
Melby et al (100)	1080	AS undergoing surgery	RHC	SPAP>35 mmHg	47%
Khandhar et al (95)	506	Severe AR	DE	RSVP>60 mmHg	16%

AS(R), Aortic stenosis(regurgitation); SPAP, Systolic pulmonary artery pressure; mPAP, mean pulmonary arterial pressure; PVR, Pulmonary vascular resistance; RVSP, Right ventricular systolic pressure; TPG, Transpulmonary gradient.

1.5. Predictors of hospitalizations for heart failure and mortality in patients with pulmonary hypertension due to left heart disease

This section is available as a research publication in the peer-reviewed journal **British Medical Journal Open.**

Dzudie A, Kengne AP, Thienneman F, et al Predictors of hospitalisations for heart failure and mortality in patients with pulmonary hypertension associated with left heart disease: a systematic review. BMJ Open 2014;4:e004843. doi:10.1136/bmjopen-2014004843.

BMJ Open

Predictors of hospitalisations for heart failure and mortality in patients with pulmonary hypertension associated with left heart disease: a systematic review

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ABSTRACT

Objectives: Left heart disease (LHD) is the main cause of pulmonary hypertension (PH), but little is known regarding the predictors of adverse outcome of PH associated with LHD (PH-LHD). We conducted a systematic review to investigate the predictors of hospitalisations for heart failure and mortality in patients with PH-LHD.

Design: Systematic review.

Data sources: PubMed MEDLINE and SCOPUS from inception to August 2013 were searched, and citations identified via the ISI Web of Science.

Study selection: Studies that reported on hospitalisation and/or mortality in patients with PH-LHD were included if the age of participants was greater than 18 years and PH was diagnosed using Doppler echocardiography and/or right heart catheterisation. Two reviewers independently selected studies, assessed their quality and extracted relevant data.

Results: In all, 45 studies (38 from Europe and USA) were included among which 71.1% were of high quality. 39 studies were published between 2003 and 2013. The number of participants across studies ranged from 46 to 2385; the proportion of men from 21% to 91%; mean/median age from 63 to 82 years; and prevalence of PH from 7% to 83.3%. PH was consistently associated with increased mortality risk in all forms of LHD, except for aortic valve disease where findings were inconsistent. Six of the nine studies with data available on hospitalisations reported a significant adverse effect of PH on hospitalisation risk. Other predictors of adverse outcome were very broad and heterogeneous including right ventricular dysfunction, functional class, left ventricular function and presence of kidney disease.

Conclusions: PH is almost invariably associated with increased mortality risk in patients with LHD. However, effects on hospitalisation risk are yet to be fully characterised; while available evidence on the adverse effects of PH have been derived essentially from Caucasians.

Strengths and limitations of this study

- Our search strategy was likely limited by its focus on a full-report article published in English and French, and traceable via PubMed MEDLINE and/or SCOPUS.
- Important heterogeneity in the included studies precluded the pooling of data to perform a meta-analysis.
- This is the first systematic review on determinants of hospitalisations and mortality in patients with pulmonary hypertension associated with left heart disease, which presents the available up-to-date and high-quality evidence on the subject matter.

INTRODUCTION

Pulmonary hypertension (PH) describes a group of disorders resulting from an increase in pulmonary vascular resistance, pulmonary blood flow, pulmonary venous pressure or a combination of these features.[1] Based on shared pathological and haemodynamic characteristics, and therapeutic approaches, five clinical groups of PH have been distinguished[2] with PH associated with left heart disease (PH-LHD) or PH group 2 credited to be the most frequent form of PH in contemporary clinical settings.[3] Indeed, PH is common in patients with LHD, where it often reflects the background LHD, but has also been reported to be a maker of disease severity and unfavourable prognosis. Patients with PH-LHD have more severe symptoms, worse tolerance to effort, experience higher hospitalisation rates and are more likely to receive an indication of the need for cardiac transplant[3] with major implications for the quality of life of patients and healthcare costs. Several studies have reported PH-LHD

to be associated with increased mortality, both in patients with systolic dysfunction and those with preserved left ventricular ejection fraction (LVEF).[3–6] Furthermore, the presence of preoperative PH has been associated with poor outcomes in patients with valve disease undergoing valve replacement.[7] However, there are still several gaps in the existing evidence, including the prevalence of PH-LHD and measurement of the true impact of PH on symptoms and outcome of various LHDs. Equally, little is known regarding the effect of the severity of PH on hospitalisations, rehospitalisations and death, and their co-factors in patients with LHD. Considering the number of recent advances in the management of PH, it is likely that a better understanding of the impact of PH-LHD on major outcomes might assist the clinical management of patients with PH.

We performed a systematic review of the existing literature to determine the predictors of hospitalisation and mortality in patients with PH secondary to LHDs including systolic dysfunction, diastolic dysfunction and/or valve disease. Additionally, we aimed to assess whether the severity of PH affects the risk of the two outcomes.

METHODS

We searched MEDLINE via PubMed and SCOPUS from inception to August 2013 for all published studies on PH-LHD, using a combination of key words described in the online supplementary box 1. All searches were restricted to studies in humans published in 'English' or 'French' languages. In addition, we manually searched the reference lists of eligible studies and relevant reviews, and traced studies that had cited them through the ISI Web of Science for any relevant published and unpublished data. Two independent reviewers (AD and APK) performed the study selection, data extraction and quality assessment; and disagreements were resolved by consensus or consulting a third reviewer (KS).

Studies that reported on hospitalisation and/or mortality in patients with PH-LHD were included if the following criteria were met: (1) age of participants greater than 18 years; (2) Right ventricular systolic pressure (RVSP) measured by transthoracic Doppler echocardiography (DE) and calculated from the maximum tricuspid regurgitation jet velocity using the modified Bernoulli equation ($4v^2$) and adding right atrial pressure (RAP). RAP could be a fixed value from 5 to 10 mm Hg, could have been estimated clinically using the jugular venous pressure (JVP), or estimated by measuring the inferior vena cava size and change with spontaneous respiration using echocardiography; and/or (3) mean pulmonary artery pressure (mPAP) measured by right heart catheterisation (RHC) or by DE. We excluded narrative reviews and case series. Studies on persistent PH following heart transplantation were not included because of the complexity of the classification of PH in this population.

The following variables were extracted from each study: publication year, country of origin of the study, study design, study population's demographics, the mean/median follow-up duration, the outcome predicted, the proportion of measurable RVSP, the mean/median baseline RVSP or mPAP, the prevalence of PH, the readmission rate, the mortality rate with odds ratio (OR) or hazard ratio (HR) for PH where reported and the predictors of outcome including the tricuspid annular plan systolic excursion (TAPSE). One study[8] reported the effect of PH in relation with survival. Effects on mortality were obtained by taking the inverse of the HR for survival.

Quality assessment

The methodological quality of the selected studies was assessed using the Quality In Prognosis Studies (QUIPS) tool, designed for systematic reviews of prognostic studies through an international expert consensus (table 1).[52] The QUIPS contains six domains assessing the following: (1) bias due to patient selection; (2) attrition; (3) measurement of prognostic factors; (4) outcome measurement; (5) confounding on statistical analysis and reporting results; and (6) confounding on presentation. In prognosis studies designed to predict a specific outcome based on a combination of several possible prognostic factors, confounding is not an issue. Therefore, the items on confounding were considered irrelevant for our quality assessment. The remaining 17 items of the five categories each were scored to assess the quality of the included studies. For each study, the five domains were scored separately as high (+), moderate (±) or low (−) quality (ie, presenting a low, moderate or high risk of bias, respectively). To strengthen the discriminative capacity of the QUIPS, we used the scoring algorithm developed by de Jonge et al,[53] as explained, described in detail in the online supplementary table.

Data synthesis

Hospitalisations or rehospitalisations for heart failure and mortality identified by multivariable analysis in individual studies are presented (table 2), including their estimated effect size (eg, OR or HR) and 95% CI. Quantitative analysis of results was not done due to important heterogeneity in study design, study population, PH definition and measurement, outcome definitions in the studies and confounding or other types of prognostic factors. We have therefore presented a narrative summary of the available evidence (table 2).

RESULTS

Studies selection

Figure 1 presents a flow diagram for the study selection process. Of the 7550 citations identified through searches, 6255 titles were examined and 6083 were excluded on the basis of the title scanning. The remaining 172 abstracts were examined and 55 articles were

Table 1 Results of quality assessment of studies on mortality and readmissions for heart failure in patients with pulmonary hypertension associated with left heart disease

N	Study	Country/ethnicity	Design	Statistical methods	Study participation	Study attrition	Measurement of prognostic factors	Assessment of outcomes	Statistical analysis and presentation	Quality score (points)	Quality: +=high ±=moderate −=low
1	Merlos et al [9]	Spain	Prospective hospital based cohort	KM, Cox regression	13.5	15	10	15	15	68.5	+
2	Agarwal et al [10]	USA—ethnicity data in 98 patients (63% whites)	Retrospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	63.5	+
3	Agarwal [11]	USA—96% blacks	Prospective hospital based cohort	KM, Cox regression	12	10	10	15	15	62	+
4	Aronson et al [12]	USA	Prospective hospital based cohort	Cox regression	15	15	15	15	12.5	72.5	+
5	Bursi et al [13]	USA Caucasians and blacks	Prospective population based cohort study	KM, Logistic regression	15	12.5	12.5	12.5	15	65	+
6	Strange et al [14]	Armadale-Australia	Retrospective population based cohort	KM, Logistic and Cox regression	15	7.5	10	12.5	12.5	58.5	±
7	Mutlak et al [15]	USA	Prospective hospital based cohort	KM, Logistic and Cox regression, KM	13.5	15	10	15	15	69	+
8	Tatebe et al [16]	Japan	Prospective hospital based cohort	KM, Logistic and Cox regression	15	10	15	15	15	72.5	+
9	Adhyapak et al [8]	India	Prospective hospital based cohort	Cox regression	13.5	10	10	12.5	5	53.5	±
10	Stern et al [17]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	15	12.5	12.5	12.5	66	+
11	Lee et al [18]	Korea	Prospective hospital based cohort	KM, Cox regression	15	15	15	12.5	15	72.5	+
12	Møller et al [19]	USA	Prospective hospital based cohort	KM, Logistic regression	13.5	15	12.5	15	15	71	+
13	Cappola et al [20]	USA, 35% blacks and 65% whites	Prospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	62.5	+
14	Szwejkowski et al [21]	UK	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	61	+
15	Abramson et al [22]	USA	Prospective hospital based cohort	KM, Cox regression	12	15	10	15	12.5	64.5	+
16	Kjaergaard et al [23]	Denmark	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+
17	Shalaby et al [24]	USA, 95% Caucasians	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	15	15	15	71	+
18	Damy et al [25]	UK	Prospective hospital based cohort	KM, Logistic and Cox regression	15	10	15	15	15	70	+
19	Ristow et al [26]	USA	Prospective hospital based cohort	Logistic regression	13.5	12.5	10	15	5	48.5	±
20	Grigioni et al [27]	Italy	Retrospective cohort	KM, Logistic regression	13.5	12.5	12.5	15	15	68.5	±
21	Levine et al [28]	USA, mainly Caucasians (78.3%)	Retrospective cohort	No Logistic regression, no KM analysis	12	10	10	7.5	2.5	42	−
22	Lam et al [29]	USA	Prospective observational community based cohort	KM, Logistic regression	12	15	10	15	12.5	68	+
23	Khush et al [30]	Multicentric USA and Canada	Prospective cohort in the ESCAPE trial	KM	15	10	15	15	12.5	68.5	+

Continued

Table 1 Continued

N	Study	Country/ethnicity	Design	Statistical methods	Study participation	Study attrition	Measurement of prognostic factors	Assessment of outcomes	Statistical analysis and presentation	Quality score (points)	Quality: +=high ±=moderate −=low
24	Ghio et al [31]	Italy	Prospective cohort	KM, Cox regression	13.5	12.5	12.5	12.5	12.5	63.5	+
25	Wang et al [32]	China	Retrospective cohort	KM	12	12.5	12.5	12.5	5	54.5	±
26	Ghio et al [33]	Italy	Prospective cohort	KM, Cox and Logistic regression	13.5	10	10	15	15	63.5	+
27	Naidoo et al [34]	South Africa, Blacks	Retrospective cohort	No Logistic regression, no Kaplan Meier analysis	12	7.5	10	5	7.5	42	−
28	Fawzy et al [35]	Saudi Arabia	Prospective cohort	No Logistic regression, no Kaplan Meier	12	10	12.5	15	7.5	57	±
29	Roseli et al [36]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	63.5	±
30	Melby et al [37]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	10	15	15	66	+
31	Le Tourneauet al [38]	France, mainly Caucasians	Prospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	63.5	+
32	Parker et al [7]	USA	Retrospective hospital based cohort	KM, Cox regression	12	15	12.5	15	15	71	+
33	Kainuma et al [39]	Japan, Asians	Retrospective hospital based cohort	KM, Cox regression	10.5	10	12.5	12.5	10	55.5	±
34	Barbieri et al [40]	Multicentric (Europe and USA)	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+
35	Manners et al [41]	United Kingdom	Retrospective hospital based cohort	No regression analysis, no KM estimation	10.5	7.5	5	5	2.5	30.5	−
36	Malouf et al [42]	USA	Prospective hospital based cohort	KM, Cox and Logistic regression	10.5	10	10	15	12.5	58	+
37	Khandhar et al [43]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	61	±
38	Zuern et al [44]	Germany	Prospective hospital based cohort	KM, Cox regression	15	7.5	10	15	15	62.5	+
39	Ben-Dor et al [45]	USA	Prospective hospital based cohort	KM, Logistic regression	15	10	10	15	15	68	+
40	Yang et al [46]	USA	Retrospective hospital based cohort	KM, Cox and logistic regression	15	7.5	15	12.5	15	65	+
41	Nozohoor et al [47]	Sweden	Retrospective cohort	KM, Cox and Logistic regression	13.5	10	10	15	12.5	61	+
42	Ward and Hancock [48]	UK	Retrospective cohort	No KM, no Logistic or Cox regression	12	5	2.5	7.5	2.5	29.5	−
43	Ghoreishi et al [49]	USA	Retrospective cohort	KM, Cox and Logistic regression	15	10	10	10	15	60	+
44	Cam et al [50]	USA	Retrospective cohort	KM, Cox and Logistic regression	13.5	15	10	10	12.5	61	+
45	Pai et al [51]	USA	Retrospective cohort	KM, Cox and Logistic regression	15	10	10	10	15	60	+

KM, Kaplan Meier.

Table 2 Study characteristics of studies on mortality and readmissions for heart failure in patients with pulmonary hypertension associated with left heart disease

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Studies in patients with heart failure and cardiomyopathies														
Merlos et al, 2013[9]	RVSP >35 mm Hg	1210 consecutive patients with HF, stratified into normal (RVSP <35), mild (RVSP 36–45), moderate (RVSP 46–60) and severe PH (RVSP >60 mm Hg)	12	72.6 54.1%	All-cause mortality Cardiovascular deaths	41.5	46	35.2	NR	NR	4.89/10 persons-year in severe PH	NA	NR	OR for mild PH 1.6 (0.7 to 3.74), moderate PH 1.34 (0.54 to 3.16) and severe PH 2.57 (1.07 to 6.27)
Agawal et al, 2012[10]	RHC with mPAP >25 mm Hg	339 patients with PH and LHD, 90% with HFpEF, NYHA class NR	54.2	63 / 21%	All-cause mortality	NA	43	NA	NR	NR	2.9%	4.4%	6.8%	UTSW cohort HR 1.4 (1.1 to 1.9) and NU cohort HR 1.4 (1.1 to 1.7)
Agawal, 2012[11]	RVSP >35	288 patients undergoing haemodialysis stratified into PH and NPH- based on RVSP	25.8	56.5 vs 53.1 / 65 vs 63%	All-cause mortality	NA	44.7 vs 27.2	38	NR	NR	26.4 vs 24.5	48.3 vs 46.3	62.9 vs 56.3	HR 2.17 (1.31 to 3.61)
Aronson et al, 2011[12]	RHC with mPAP ≥25 mm Hg and mPCWP >15 mm Hg	242 patients with acute HF, divided in 3 groups, NPH, passive PH and reactive PH, NYHA class IV	6	61; 42%	All-cause mortality	NA	34 vs 38 vs 44	76.0	NR	8.6 vs 21 vs 48.3	NR	NR	NR	HR for passive PH 1.7 (0.6 to 4.5) and reactive PH 4.8 (2.1 to 17.5)
Bursi et al, 2012[13]	RVSP >35 mm Hg	1049 patients with HF stratified into tertiles of RVSP (<41, 41–54 and >54 mm Hg)	81	76; 49.3%	All-cause mortality	NR	48	79	NA	NR	4, 10, and 17% for tertiles 1, 2, and 3, respectively	8 vs 19 vs 28	46	HR for tertile 2: 1.45 (1.13 to 1.85) and tertile 3: 2.07 (1.62 to 2.64)
Strange et al, 2012[14]	RVSP >40 mm Hg	15633 echo screening, 636 PH group 2 stratified into 3 groups (group 1 RVSP <40 mm Hg, group 2 between 41 and 60 and group 3 >60 mm Hg)	83	79; 48%	All-cause mortality	NR	52	NR	NA	NR	NR	NR	Mean survival 4.2 years	NR
Mutlak et al, 2012[15]	RVSP >35 mm Hg	1054 patients with acute myocardial infarction divided into NPH and PH groups	12	60 vs 69; 77 vs 64%	Readmission for HF All-cause mortality	NR	32 vs 43	44.6	2.1 vs 9.2; OR 3.1 (1.87 to 5.14)	NR	NR	NR	NR	HR for readmission 3.1 (1.87 to 5.14)
Tatebe et al, 2012[16]	RHC with mPAP ≥25 mm Hg mPCWP >15 mm Hg	676 consecutive patients with chronic HF, NYHA class ≥2, stratified into 3 groups, NPH (mPAP <25), passive PH (PH with PVR ≥2.5 WU) or reactive PH (PH with PVR >2.5 WU)	31.2	64vs 64vs 63; 63vs 48vs 66%	All-cause mortality and readmission for HF	NR	17 vs 30 vs 35 in NPH, passive PH and reactive PH, respectively	23	NR	NR	24.5 vs 18 vs 18.9% in NPH, passive and reactive PH, respectively	52.5 vs 50 vs 60.3% in NPH, passive and reactive PH, respectively	71.0 vs 77 vs 79.3 in NPH, passive PH and reactive PH, respectively	HR for reactive PH group 1.18 (1.03 to 1.35)
Adhyapak, 2010[8]	Echocardiography with mPAP >25 mm Hg	147 patients with HF stratified into: group 1, normal PASP/preserved RV function; group 2, normal PASP/RV dysfunction; group 3, high PASP/preserved RV function; and group 4, high PASP/RV dysfunction	11.2	54 91.8%	Cardiac death Readmissions	NR	Group 1 20±5 group 2 24.8 ±0.4 group 3 56.8±6 and group 4 58.9 ±8.8	53.7	19.7, OR and CI NR		Overall 5.1 at 11.2 months, 4.5 in group 3 vs 8.8 in group 4	NA	NA	HR in PH 2.27 (1.09 to 3.57)

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Stern et al, 2007[17]	Echocardiography but criteria for PH not reported	68 patients needing cardiac resynchronisation stratified into group 1 (RVSP ≥ 50 mm Hg, n=27) and group 2 (RVSP <50 mm Hg, n=41)	7.1	70 64.7%	Composite of hospitalisation for HF and all-cause mortality	NR	Group 1 39.7 ±6.7 and group 2 60.2±9.2	NR	NR	NR	Increased mortality in patients with RVSP ≥50 mm Hg	NR	NR	HR of 2.0 (1.2 to 5.5) for RVSP ≥50
Lee et al, 2010[18]	RVSP >39 mm Hg	813 patients with TR stratified into two groups based on the RVSP <39 mm Hg (group 1, n=530) and RVSP ≥39 mm Hg (group 2, n=283)	58.8	64 42.5%	All-cause mortality	NR	37.1 in patients who survived vs 43.8 in patients who died	NR	NR	NR	NR	10.5 vs 21.9	5-year survival rates 61.0 and 80.6% group 2 vs group 1 respectively	HR of 1.024 (1.017 to 1.032)
Møller et al, 2005[19]	RVSP >30 mm Hg	536 patients with acute myocardial infarction stratified into group 1 (RVSP <30 mm Hg), group 2 mild to moderate PH (RVSP of 31 to 55 mm Hg) and group 3 severe PH (RVSP >55 mm Hg)	40	65/ 68% 74/54% 78/44% in groups 1, 2 and 3, respectively	All-cause mortality	69	NR	75	NR	NR	NR	5% in group 1 52% in patients with a RVSP >65 mm Hg	NR	HR 1.22 (1.14 to 1.38) per 10 mm Hg increased
Cappola et al, 2012[20]	RHC with mPAP ≥25 mm Hg	1134 patients with cardiomyopathy stratified according to PVR: NPH (<2.5), group 1 PH (2.5–3), group 2 PH (3–3.5), group 3 PH(3.5–4) and group 4 PH (>4)	52.8	48 60%	All-cause mortality	NA	25	NR	NR	NR	NR	NR	33% of patients died during the mean FU	HR 1.86 (1.30 to 2.65) for group 2, 1.78 (1.13 to 2.81) for group 3 and 2.04 (1.51 to 2.74) for group 4
Szwejkowski et al, 2011[21]	RVSP >33 mm Hg	1612 patients with HF stratified into 5 groups according to RVSP (<33; 33–38; 39–44; 45–52 and >52 mm Hg)	33.6	75.2 57.4%	All-cause mortality	32	46	83.3	NR	NR	NR	NR	55.1% of patients died during the mean FU	HR 1.06 (1.03 to 1.08) for every 5 mm Hg increase in RVSP
Abramson et al, 1992[22]	Echocardiography with TRV >2.5 m/s	108 patients with dilated cardiomyopathy, stratified into 2 groups: group 1 (TRV <2.5 m/s) and group 2 (>2.5 m/s), 38.9% in NYHA class III and IV, 77.3% of ischaemic HF	28	67.5 81%	All-cause mortality, mortality due to HF and re-hospitalisations for HF	NR	5.6 m/s	26	75% during the study period 5.76 (1.97 to 16.90)	NR	NR	NR	17% in 28 months vs 57%	OR for increased TRV 3.77 (1.38 to 10.24)
Kjaergaard et al, 2007[23]	Echocardiography but cut-off for PH not reported	388 consecutive patients with known or presumed HF stratified into quartiles of RVSP (<31, 31–38, 39–50, >50)	33.6	75 60%	All-cause mortality	NR	38	75% and 50% with RVSP >31 and 40 mm Hg, respectively	NR		48% if COPD and 21% in HF without COPD	NR	57% at 33.6 months	HR 1.09 (1.04 to 1.14) for every increase of RVSP per 5 mm Hg
Shalaby et al, 2008[24]	RVSP ≥30 mm Hg	270 patients undergoing cardiac resynchronisation stratified into 3 groups on the basis of RVSP: group 1, (22–29, n=86); group 2 (30–44, n=90) and group 3 (45–88, n=94).	19.4	66.5 91%	All-cause mortality, cardiac transplantation (primary end point) or re-hospitalisation for HF	NR	40.4	NR	40% in group 3 vs 9% in group 1 (6.35 (2.55 to 15.79))	NR	NR	NR	12% in group 1% vs 34% in group 3 at mean follow-up	HR 2.62 (1.07 to 6.41)

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Damy et al, 2010[25]	Echocardiography with RVTG >25 mm Hg	1380 patients with congestive HF, 1026 with LVSD (EF <45%) and 324 without), further stratified into quartiles of RVSP	66	72 67%	All-cause mortality	30% of all, 26% in patients with LVSD and 40% in those without	25	46% of HFpEF,50% of HFrEF and 23% of patients without HF	NA (outpatient cohort)	NR	NR	NR	40.3% at median follow-up of 66 months	HR 1.72 (1.16 to 2.55) for RVSP >45 mm Hg)
Ristow et al, 2007[26]	Echocardiography with TR gradient >30 mm Hg	717 patients with coronary artery disease, 573 with measurable TR, stratified into group 1 (TR gradient ≤30 mm Hg, n=447) and group 2 (TR gradient >30 mm Hg, n=126)	36	65, 74% (group 1) 69, 75% (group 2)	Hospitalisation, CV death, all-cause death and the combined end point of all	80	NR	22	6% (group I) vs 21% (group II) OR per each 10 mm Hg increase of TR gradient 1.5 (1.03 to 2.2)	NR	NR	NR	11% (group 1) vs 17% (group 2)	OR for all-cause deaths 1.2 (0.85 to 1.6) per 10 mm Hg increase in TR OR for combined endpoint 1.6 (1.1 to 2.4)
Grigioni et al, 2006[27]	RHC with mPAP ≥25 mm Hg	196 patients with HF evaluated for PH and changes in mPAP	24	54 73%	Cardiovascular deaths, acute HF and combined end point of both	NA	25	NR	27% acute HF, 2.30 (1.42 to 3.73)	NR	NR	20% cardiovascular deaths	NR	HR for PH 2.3 (1.42 to 3.73) ; HR for worsening >30% in mPAP 2.6 (1.45 to 4.67)
Levine et al, 1996[28]	RHC assessed change in PH, no definition	60 patients with PH owing to HF awaiting heart transplantation, stratified into 2 groups: group A (persistent elevated sPAP, n=31), group B (decrease in sPAP, n=29)	10	50 85%	Transplant or all-cause death	NA	39 vs 57 in group A and group B, respectively	NA	NR	NR	NR	NR	90% vs 50% of death at 10months in group A and group B, respectively	NR
Lam al, 2010[29]	RVSP >35 mm Hg	244 patients with HFpEF compared with 719 subjects with HTN. 203 patients with HFpEF and PH later stratified into: group 1 (RVSP <48 mm Hg) and group 2 (RVSP >48 mm Hg)	33.6	74/47% vs 79*/ 41% in group 1 and group 2, respectively	All-cause mortality	65 vs 83% in HTN and HFpEF, respectively	28 vs 48 mm Hg in HTN and HFpEF, respectively	8 vs 83% in HTN and HFpEF, respectively	NR	NR	12.2 vs 25.7 in group 1 and group 2, respectively	18.4 vs 36.2 in group 1 and group 2, respectively	55.1 vs 63.8 in group 1 and group 2, respectively	HR 1.20 per each increase of 10 mm Hg in RVSP (p<0.001)
Kush et al, 2009[30]	RHC with mixed PH (MPH) defined as mPAP ≥25 mm Hg, PCWP >15 mm Hg, and PVR ≥3 WU	171 patients with severe HFrEF (NYHA class IV, LVEF ≤30%,systolic BP ≤125 mm Hg) further stratified into 2 groups: MPH group (mPAP >25 mm Hg and PVR >3 WU, n=80) and non-MPH (mPAP <25 mm Hg or PVR <3WU, n=91)	6	59/75% vs 54*/ 71% in MPH and non-MPH, respectively	Rehospitalisations and all-cause mortality	NA	mPAP: 42 vs 32 in MPH and non-MPH, respectively TPG:17 vs 7, respectively	47	HR for MPH 0.8 (0.59 to 1.08)	21 vs 22	NR	NR	NR	HR for MPH 0.89 (0.66 to 1.20)
Ghio et al, 2001[31]	RHC with mPAP ≥20 mm Hg, RV systolic dysfunction defined as RVEF <35%	377 patients with HF stratified into: group 1, normal mPAP/preserved RVEF (n=73); group 2 normal mPAP/low RVEF (n=68); group 3, high PAP/ preserved RVEF (n=21); and group 4, high PAP/low RVEF (n=215)	17.2	51 85.7%	Heart transplantation and all-cause mortality	NA	27.9	62.3	NR	NR	NR	NR	7.3 vs 12.3 vs 23.8 vs 40 in groups 1, 2, 3 and 4,* respectively	HR 1.1 (1.0 to 1.21) per each 5-mm Hg increment

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Wang et al, 2010[32]	RVSP >30 mm Hg	93 patients with HF undergoing cardiac resynchronisation stratified into group 1 (RVSP >50 mmH, n=29); group 2 (30 <RVSP ≤50 mm Hg, n=17) and group 3 (RVSP ≤30 mm Hg, n=47)	32 (6 to 60)	59.6 81.7%	All-cause mortality, HF mortality	NR	NR	49.5	NR	28 vs 6 vs 17% in groups 1,2 and 3, respectively	NR	NR	NR	Non-significant increased in all-cause mortality (p=0.33), increase in HF mortality but OR/ HR not reported
Ghio et al, 2013[33]	RVSP >40 mm Hg and RV dysfunction defined as TAPSE <14 mm	658 patients with chronic HF stratified into group 1 (no PH no RVD, n=256), group 2 (RVD, no PH, n=54), group 3 (PH, no RVD, n=167), and group 4 (RVD and PH, n=67)	38	63 86%	All-cause mortality, urgent cardiac transplantation or ventricular fibrillation	83	38	35.6	NR	17.5% in PH vs 4.5% in non-PH	21.4% in PH vs 8.7% in non-PH	42.3% in PH vs 20.3% in non-PH	59.4% in PH vs 45.2% in non-PH	HR 1.90 (2.18 to 3.06) for group 3 and 4.27 (3.45 to 7.43) for group 4
Studies in patients with heart valve disease														
Fawzy et al, 2004[35]	Severe PH defined as RVSP >50 mm Hg	559 patients with MS undergoing MBV stratified into three groups: group A (RVSP <50 mm Hg; n=345); group B (RVSP 50–79 mm Hg; n=183) and group C (RVSP ≥80 mm Hg; n=31)	63.6	31/28.1% vs 30/25.1% vs 27/16.1% in groups A, B and C, respectively	Reversibility of PH following MBV	NR	38.5 vs 59 vs 97.8 in groups A, B and C, respectively	62% vs 33% vs 5% for groups A, B, and C, respectively	NR	0	0	0	0	No mortality was encountered, PH normalised over a 6 to 12 months
Naidoo et al, 1991[34]	RHC with PASP ≥30 mm Hg	139 patients with AR (69 undergoing AVS) stratified into group 1 (normal or mild PH) and group 2 (moderate PH or marked PH)	6	32.9 vs 36.2 and 69.7 vs 77.8 in group 1 and 2, respectively	Immediate and 6 months postoperative mortality	NA	18 vs 43.7 in group 1 and 2, respectively	63.3	NR	3 in group 1 vs 2.8% in group 2	NR	NR	NR	No increased in mortality, HR not reported
Manners et al, 1977[41]	RHC with PASP >70 mm Hg	392 patients who had undergone prosthetic valve surgery stratified into 2 PASP <70 mm Hg, n=336 or PASP >70 mm Hg, n=56)	48	NR	Hospital mortality	NA	Mean PASP was 93 mm Hg	NR	NR	NR	NR	NR	5.4% at 4 years in both PH and non-PH	NR
Roseli et al, 2002[36]	RVSP >35 mm Hg	2385 patients undergoing AVR stratified into 3 groups: RVSP <35 mm Hg n=611; RVSP 35–50 mm Hg, n=1199; RVSP >50 mm Hg, n=575	51.6	74 55%	All-cause hospital and late mortality	NR	41	74	NR	15.8 vs 19.7 vs 25.9	NR	NR	NR	Higher RVSP was predictor of 5 and 10 years mortality, HR not reported
Melby et al, 2011[37]	RVSP >35 mm Hg	1080 patients with AS undergoing AVR, stratified into NPH, (RVSP <35 mm Hg, n=574) and PH group(mild PH, moderate and severe PH)	48	72.3 vs 70.2 59.1 vs 57.8% in PH and non PH, respectively	All-cause operative and long-term mortality	NR	51 in PH group	46.8	NR	NR	17.1 vs 17.6 vs 17.1 vs 23.5 for non-PH, mild, moderate and severe PH, respectively	25.7 vs 24 vs 23.2 vs 32.3	25.7 vs 38.4 vs 52.7 vs 46.1	OR 1.51 (1.16 to 1.96), persistent PH after AVR was associated with decreased survival
Le Tourneau et al, 2010[38]	RVSP ≥50 mm Hg	256 patients with MR undergoing MVO, stratified into group 1 (RVSP <50 mm Hg, n=174) and group 2 (RVSP ≥50 mm Hg, n=82)	49.2	63 66%	All-cause mortality Cardiovascular deaths	NR	45±14	32% had RVSP ≥50 mm Hg	NR	NR	NR	31.6 vs 31.7 in groups 1 and 2, respectively	NR	HR 1.43 (1.09 to 1.88) per 10 mm Hg increment of RVSP

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Parker et al, 2010[7]	RVSP >35 mm Hg	1156 patients with MR or AR stratified into normal (RVSP <30 mm Hg), borderline (31–34 mm Hg), mild (35–40 mm Hg) or moderate or greater (>40 mm Hg)	87.6	72 51%	All-cause mortality	52	29	NR	NR	NR	NR	NR	NR	HR for moderate or greater PH 1.95 (1.58 to 2.41) in AR and 1.48 (1.26 to 1.75) in MR
Barbieri et al, 2010[40]	RVSP >50 mm Hg	437 patients with MR, 35% NYHA class III or IV, normal LVEF, stratified into NPH (RVSP ≤50 mm Hg) and PH (RVSP >50 mm Hg)	57.6	67 66%	All-cause mortality, cardiovascular death, heart failure		45	23	1.70 (1.10 to 2.62) and 1.19 (1.06 to 1.35) for each 10 mm Hg increase of RVSP	NR		NR	23% at the mean follow-up	HR 2.03 (1.30 to 3.18) and 1.16 (1.03 to 1.31) for each 10 mm Hg increase of RVSP
Kainuma et al, 2011[39]	Echocardiography, PH definition not specified	46 patients undergoing MVR, NYHA III or IV, LVEF <40%, stratified into group 1 (RVSP <40 mm Hg, n=19), group 2 (moderate PH (40 <RVSP <60, n=17) and group 3 (RVSP >60, n=10)	36	64 35%	Cardiac death, myocardial infarction, endocarditis, thromboembolism, reoperation for recurrent MR, readmission for heart failure and fatal arrhythmia	NR	47	NR	30% in the severe PH but not significant, OR and CI NR	NR	15.8 vs 11.8 vs 20% for groups 1, 2, and 3, respectively	31.6 vs 29.4 vs 30%	47.4 vs 82.4 vs 50%	HR for all adverse cardiac events 6.9 (1.1 to 44) in group 3
Khandhar et al, 2009[43]	Severe PH defined as RVSP >60 mm Hg	506 patients with severe AR stratified into group 1, severe PH with RVSP >60 mm Hg, n=83 and group 2 (RVSP <60, n=423), NYHA NR	NR	63 47%	All-cause mortality	100	NR	16% of severe PH	NR	NR	NR	21.6 of patients with severe PH	NR	PH was associated with increased mortality in all groups, OR and CI NR
Malouf et al, 2002[42]	Severe PH defined as peak TRV ≥4 m/s	3171 patients with AS of whom 47 with severe PH, stratified into group 1 (no AVR, n=10) and group 2 (AVR, n=37), 79% in NYHA III and IV	15.3	78 47%	All-cause mortality	63% of the 3171 total population of patients with aortic stenosis	4.16 m/s	NA	NR	NR	NR	NR	80% vs 32% in groups 1 and 2, respectively, at median FU	OR for mortality risk in severe PH and AVS 1.76 (0.81 to 3.35)
Zuern et al, 2012[44]	RVSP >30 mm Hg	200 patients with AS undergoing AVR stratified into NPH (RVSP <30) vs mild-to-moderate PH (30 <RVSP <60) and severe PH (>60 mm Hg)	31.2	72.3 52.5%	All-cause mortality	NR	36.3	61	NR	NR	10.2 vs 14.1 vs 30.4	30.7 vs 40.4 vs 60.1	2.6, 15.2 and 26.1%	HR for mild-to-moderate PH 4.9 (1.1 to 21.8) and severe PH 3.3 (0.6 to 19.7)
Ben-Dor et al, 2011[45]	RVSP >40 mm Hg	509 patients with AS divided into group 1 (RVSP <40 mm Hg, n=161); group 2 (RVSP 40–59, n=175) and group 3 (RVSP >60 mm Hg, n=173)	6.73	82.3 vs 82.4 vs 80.5 in groups 1, 2 and 3, respectively, >75%	All-cause mortality	NR	33.7 vs 49.3 vs 70.7 in groups 1, 2, and 3, respectively	68.3	NR	NR	NR	NR	21.7 vs 39.3 vs 49.1 in groups 1, 2 and 3, respectively at median FU*	PH was significantly associated with increase in mortality, OR/HR not reported
Yang et al, 2012[46]	RVSP >40 mm Hg	845 patients who underwent valve surgery and/or CABG (444 without PH or NPH vs 401 PH), all with LVEF <40%	39	65.2 vs 67.8 78.8 vs 72.6% in NPH and PH group, respectively	Postoperative complications and mortality		NR	NR	NR	NR	4.6 vs 13.9 in NPH vs PH group, respectively	NR	16.7 vs 30.6* in NPH vs PH group, respectively	OR for mild/ moderate PH 1.475 (1.119 to 1.943)

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Nozohoor et al, 2012[47]	RVSP >50 mm Hg	270 patients with MR undergoing MVS, stratified into NPH group (RVSP <50 mm Hg) and PH group (RVSP ≥50 mm Hg)	61.2	61.5 vs 66.5 70 vs 54% in no PH and PH group, respectively	Perioperative complications and all-cause late mortality	NR	NR	27	NR	NR	7.6 vs 8.2 in no PH and PH, respectively	22.4 vs 17.6 in no PH and PH, respectively	31.1 in both groups	HR 4.3 (1.1 to 17.4) during the initial 3 years after MVS
Ward and Hancock 1975[48]	RHC with extreme PH defined as SPAP >80 mm Hg and PVR >10 WU: 8.2%	Mitral valve disease (n=586), 48 extreme PH stratified into group 1 (no operation), group 2 (all surgical) and group 3 (survive after surgery)	69.6	46.2 vs 42.4 43 vs 29% in group 1 and 2 respectively	All-cause mortality	NA	105 vs 96.6	8.2	NA	NR	NR	NR	NR	Extreme PH was associated with higher mortality, and surgery improved survival
Ghoreishi et al, 2012[49]	sPAP >40 mm Hg using RHC in 591 patients and RVSP >40 mm Hg using DE	873 patients with MR who underwent MVS, stratified into NPH and PH group (mild, moderate, severe) NHYA not reported	35	59 59%	Hospital mortality, Late all-cause mortality	NR	46 (echo), and sPAP was 43 by RHC	53	NR	NR	16.2 in non PH vs 32% in PH group*	33.9 in non PH vs 48.1% in PH group*	51.8 in non PH vs 60.9% in PH group*	HR 1.018 (1.007 to 1.028) per each 1 mm Hg increment in RVSP
Cam A et al, 2011[50]	RHC with severe PH defined as mPAP >35 mm Hg	317 patients with AS, 35 with severe PH underwent surgery and were compared to 114 mild moderate PH and to 46 severe PH treated conservatively, NHYA not reported	11.3	71/53.5 (mild-moderate PH) vs 75/51.4 (severe PH)	All-cause mortality	NA	22.5 (mild-moderate PH) vs 45.3 (severe PH)	47.0	NR	NR	NR	NR	74.5 vs 75.5	HR 1.008 (0.9 to 1.11) and early postoperative reduction in mPAP 0.93 (1.2 to 12.5)
Pai et al, 2007[51]	Severe PH defined as RVSP >60 mm Hg	116 patients (of 740 severe AS) with severe PH among which 36 underwent AVR and were compare to 83 remaining	18	75 39%	All-cause mortality	NR	69	15.7% (severe PH)	NR	NR	NR	30.5 (PH) vs 15.5 (NPH)	NR	AVR benefit HR 0.28 (0.16 to 0.51) independent of PH

*p<0.05.

AS(R), aortic stenosis (regurgitation); AVS(R), aortic valve surgery (replacement); CABG, coronary artery bypass graft; DE, Doppler echocardiography; eSPAP, estimated systolic pulmonary artery pressure; HFpEF, heart failure (HF) and preserved ejection fraction; LHD, left heart disease; LVEF, left ventricular (LV) ejection fraction; MBV, Mitral Balloon Valvotomy; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; MV(R/O), mitral valve (repair/operation); NA, not applicable; NPH, non-pulmonary hypertension; NR, not reported; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV(SP/TG), right ventricular systolic pressure/tricuspid gradient); TPG, transpulmonary gradient; TRV, tricuspid regurgitation (TR) velocity(TRV); TAPSE, tricuspid annular plan systolic excursion; UTSW, University of Texas—Southwestern; WU, wood units.

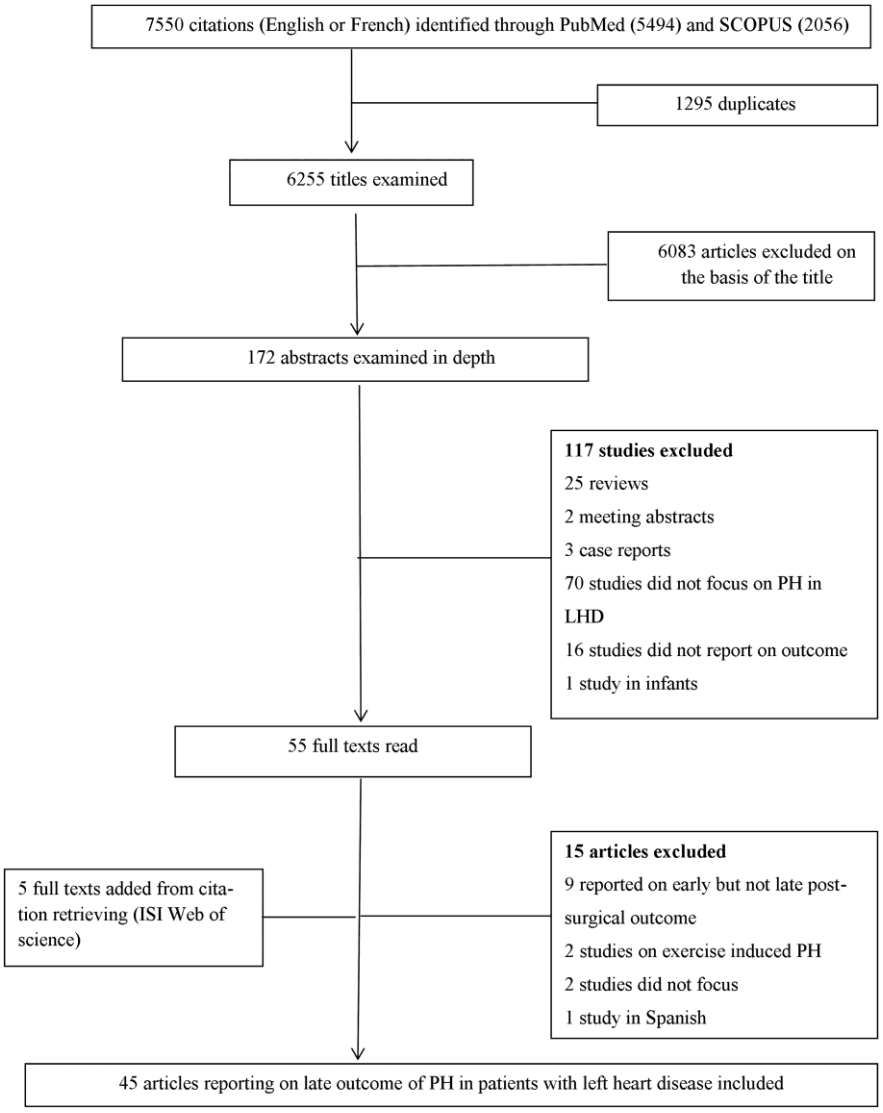

Figure 1 Flow diagram of literature search process. LHD, left heart disease; PH, pulmonary hypertension.

screened by full text of which 15 were excluded for various reasons (figure 1). Five studies were identified via citation search. Therefore, 45 articles were included in the final review among which 86.7% were published between 2003 and 2013 (see online supplementary figure S1).

Study characteristics and methodological quality

The characteristics and methodological quality of the 45 included studies are described in table 1. The overall quality score ranged from 29.5 to 72.5 points with a median of 63.5. Based on the cut-offs of ≥60 and ≥45 points, respectively, we classified 34 articles as being of high quality, 7 as moderate-to-high quality and four as low-quality studies (table 1). Studies of high quality were recent and scored well on patient selection, outcome measurement, statistical analysis and presentation. Studies classified as moderate/low quality scored relatively well on patient selection, but poorly on study attrition, statistical analysis and presentation. Twenty-four (53.3%) studies were from the USA, 12 (26.6%) from Europe (four from UK, three from Italy and one each from Spain, Germany, Denmark, France and Sweden), 6 (13.3%) from Asia (two from Japan, one each from India, China, Korea and Australia) and 1 from South Africa. One study was multicentric across Europe and the USA[40] and another one was multicentric across the USA and Canada.[30] Only three population-based cohorts were reported including two prospective[13 29] and one retrospective study.[14] For the remaining 42 hospital-based cohort studies, 20 had a retrospective design. The number of participants ranged from 46 to 2385 in hospital-based and from 244 to 1049 in population-based studies. The proportion of men ranged from 21% to 91%, and mean/median age from 63 to 82 years. Twenty-six studies were in patients with heart failure (HF) and cardiomyopathies (two in heart failure with preserved ejection fraction (HFpEF)) and 19 in patients with valve disease.

Twelve studies defined PH using RHC and 32 studies using DE. One study defined PH using both RHC and DE. Studies applied variable definitions of PH using both

RHC (based on mPAP >25 or 30 mm Hg, or on systolic pulmonary artery pressure (sPAP) >50 mm Hg, or sPAP >40 mm Hg, or on pulmonary vascular resistance (PVR) >2.5 wood units (WU)) and DE (based on RVSP with cut-offs varying from 35 to 50 mm Hg, or based on a mPAP >25 mm Hg[8] or on a right ventricular tricuspid gradient (RVTG) >25 mm Hg).[25] Prevalence of PH in HF ranged from 22% to 83.3% overall, 22–83.3% in studies of PH based on DE and 23–76% in studies of PH based on RHC (see online supplementary figure S2).

Outcome of PH

Admissions for heart failure

The duration of follow-up ranged from 6 to 87.6 months overall, 6–69.6 months in studies of PH based on RHC definition and 6–87.6 months in studies of PH based on DE definition. Readmission rates, when reported, ranged from 9.2% to 75% overall and 9.2–75% in studies of PH based on DE definition. Only one study with PH definition based on RHC reported a readmission rate of 27% (table 2). Admissions or readmissions for HF were reported in nine studies all based on DE definition among which seven reported HRs or ORs for admission/readmission in relation with PH. Effect estimates for six of the seven studies were statistically

Mortality

Mortality was reported in all studies (table 2); however, not all studies provided multivariable-adjusted effect estimates of mortality risk associated with PH. PH was associated with increased all-cause mortality in 24 of 26 studies of HF, among which 6 studies were of PH based on RHC definition, while two studies failed to report an association between PH and all-cause mortality at 6 months. Of these two studies, one used PH definition based on RHC and was a multicentric trial of HF that reported effect estimates for mortality risk from PH (HR=0.89 (95% CI 0.66 to 1.20));[30] while the other one[32] did not. When reported, mortality rates at 12 months ranged from 0% to 32% overall, 0% to 32% in studies of PH based on DE and 2.9% to 18% in studies of PH based on RHC (see online supplementary figure S3). As summarised in table 3, over 35 potential predictors of mortality were tested across studies with variable and often inconsistent effects on the outcome of interest. Age was associated with mortality in 14 studies (among which 11 studies of PH were based on DE), male gender in 3/11 studies (all based on DE), LVEF in 6/10 studies, right ventricular (RV) function in 3/3 studies and renal disease (rising creatinine, decreasing glomerular filtration rate (GFR) or dialysis) in 6/17 studies (all based on DE), functional class (New York Heart Association (NYHA) or WHO) in 7/12 studies (five based on DE) while the 6 min walking distance was tested in only one study but was not integrated in the multivariable analysis for outcome risk.[32]

DISCUSSION

An increasing number of studies have assessed the risk of readmission and mortality in patients with LHD-related PH over the last decade, and mostly in North America and Europe. Available studies are mostly consistent on the adverse effect of PH (whether assessed using DE or RHC) on mortality risk in patients with heart failure as well as those with mitral valve disease, but less unanimous in those with aortic valve disease. The consistent adverse effect of PH in this population highlights the importance of early diagnosis of PH to reduce mortality. While available studies have been overall of acceptable quality, substantial heterogeneity in the study population, PH definition and measurement, outcome definitions as well as other prognostic factors limit direct comparisons across studies. Information on readmission for heart failure was limited and the assessment of other prognostic factors in an integrated multivariable model was very heterogeneous.

Mortality in patients with PH and heart failure with reduced ejection fraction

While PH was an independent prognostic factor for mortality in fatal-outcome studies, the prevalence of PH and effects on mortality varied according to LVEF. Differences in the prevalence of PH could be explained at least in part by population heterogeneity (age, level of HF, HF centres or community study) and differences in the criteria used to define PH across studies with a variety of cut-off values. Regardless of the prevalence of PH in HFrEF, there seems to be no uniformity in the association between the magnitude of reduction in LVEF, and the presence or absence of PH and the effects of PH on mortality risk. It is possible that the small size of studies and the short duration of follow-up precluded the accumulation of a substantial number of events to allow the detection of a relationship, if any. Furthermore, although the precise haemodynamic threshold beyond which RVSP is invariably associated with mortality is subject to debate; the risk of death associated with PH seems to increase with higher RVSP.[6 12 13 16] A possible pathophysiological explanation is that early and higher vascular remodelling occurs in patients with HF and severe PH, causing a reactive or 'postcapillary PH with a precapillary component', which in turn has a greater impact on the RV function. Equally, RV systolic function has been shown to be highly influenced by pressure overload and by vascular resistance in the pulmonary region[50]; and RV function assessed using RHC or echocardiography has been shown to be associated with mortality.[30 31 33] It is, however, remarkable that one study[30] reported no interaction between PH and RV function, with both variables being independently associated with mortality. This highlights the fact that RV function in HF does not only depend on pulmonary pressure but may also reflect intrinsic myocardial disease. As suggested by Vachiery et al[6] there might be a spectrum of clinical phenotypes of RV failing in PH-LHD that might evolve from one to the other, from isolated postcapillary PH with little effect on

Table 3 Other prognostic factors associated with mortality in patients with pulmonary hypertension associated with left heart disease

Factor	Number of studies reporting		Number of studies in which the factor was associated with poor outcome	
	overall	Studies based on DE	Studies of PH based on DE	Studies of PH based on RHC
Age	14	11	11	3
Sex (male vs female)	11	9	3	0
Racial/ethnic group	2	2	0	0
HF episodes	5	5	2	0
Prior hypertension	5	5	1	0
History of diabetes	8	8	3	0
Smoking	3	3	0	0
History of cardiovascular disease	1	1	1	0
Functional class (NYHA/WHO)	12	9	5	2
Killip class for MI	2	2	2	0
Heart rate	2	2	0	0
Systolic BP	4	4	2	0
Diastolic BP	1	1	1	0
Mean BP	1	1	1	0
SPO_2	3	3	1	0
Hypotension	1	1	1	0
Atrial fibrillation	5	5	5	0
Ischaemic aetiology of HF	4	4	0	0
Urea	2	2	1	0
Kidney disease (by creatinine, GFR or haemodialysis)	17	14	6	0
BNP	3	3	2	0
Haemoglobin	2	2	0	0
Presence of COPD	4	3	3	0
Use of medications (ACEI and or beta blockers or spironolactone)	6	6	3	0
LVEF	10	10	6	NA
LV end-diastolic diameter/index	6	6	3	NA
Atrial diameter	1	1	1	NA
Deceleration time	1	1	0	NA
RV function (by TAPSE or other means)	3	3	3	NA
Functional mitral regurgitation	5	5	4	NA
RVSP ≥50 or >60 mm Hg	9	9	5	NA
End diastolic pulmonary regurgitation	1	1	1	NA

ACEI, ACE inhibitors; BNP, brain natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; RHC, right heart catheterisation; RVSP, right ventricular systolic pressure; RV, right ventricle; TAPSE, tricuspid annular plan systolic excursion.

the RV to more advanced disease where the failing RV is the key determinant of outcome.

Mortality in patients with PH and heart failure with preserved ejection fraction

Over the past decades, the increasing prevalence of HFpEF[51] has been paralleled by an increasing presence of PH in patients with HFpEF.[5 6] When compared to heart failure with reduced ejection fraction (HFrEF), patients with HFpEF have their subset of risk factors; but finally, PH conveys similar morbidity and mortality risk in the two subgroups of patients.[13 17] The current incomplete understanding of HFpEF limits our ability to explain why these patients develop PH. However, it is estimated that over time left atrium and ventricular filling pressure from compromised left ventricle and, in some, left atrium relaxation and distensibility can lead to elevated pulmonary venous pressure, triggering vasoconstriction and arterial remodelling.[4 5] In total, the finding of PH as an independent prognostic factor for mortality in patients with HF tends to support the suggestion that PH should be considered as a potential therapeutic target at least in the group of patients with HF who exhibit persisting PH after optimisation of HF therapy. In this line, targeting both pulmonary vasculature and the heart would probably be more beneficial.

Mortality in patients with PH related to valvular heart disease

PH due to valvular heart disease (VHD) was not always related to mortality risk,[38 39 45] which is in contrast with PH in patients with heart failure. A simple explanation

of this difference could be that the prevalence and severity of PH correlates with the severity and type of VHD. Although mitral stenosis (MS) has been the classical disease associated with PH-LHD and reactive PH was initially described in these patients[4]; it is, however, noticeable that PH due to MS has received little attention over the last decade, probably because of the progressive decline in RHD in Western countries. Interestingly, the two studies included showed that surgery was safe and improved survival in patients with PH due to MS[35 48] with PH regressing to normal levels over 6–12 months after successful Mitral Balloon Valvotomy (MBV).[35] In mitral regurgitation (MR), nearly all cohort studies on outcomes of severe PH reported increased mortality.[38 39 40 46 49] The relevance of this finding is that PH can serve both as an indication for proceeding to surgical or catheter-based interventions, and also as an operative risk factor for mitral valve interventions.[54] By contrast, PH is not as common in the aortic valve surgical cohort. Mortality rates in different studies of patients with VHD depends on comorbidities, exclusion criteria and definition for PH. Studies that also evaluated changes in PH following valve surgery showed a decline in pulmonary pressures following surgery.[35 45 50 55] It is worth noting that the pathophysiology of the pulmonary vasculature in PH due to VHD is similar to that in patients with HF.[1]

Hospitalisations and other prognostic factors

The paucity of information on the effect of PH-LHD on hospitalisations or rehospitalisations as has been shown in this study highlights the need for more evidence on this outcome. Such information is important to fully characterise and quantify the contribution of PH-LHD to the global burden of disease, and assess future improvement from treating the underlying LHD and/or controlling PH in patients with LHD.

Of the 35 other potential prognostic factors of mortality in patients with PH that were tested in multivariable models across studies, investigations on echocardiographic parameters suggested that PH >60 mm Hg was associated with worse mortality in seven of the nine studies. Similarly, a greater degree of MR, deceleration time when reported[26] and RV function were almost constantly associated with adverse outcome while LVEF was associated with adverse outcome in 6 of the 10 studies. In the evolution of LHD, RV dysfunction usually occurs as a turning point. It shall be noted that PH incorporates information on diastolic function, MR and pulmonary vascular disease, and this might explain the pivotal role of PH in gauging the prognosis of patients with HF.

Strengths and limitations of the studies included in the review

The first limitation of the studies included in our review is the possibility of study population bias. The majority of studies originated from Western countries and included predominantly Caucasians and reported mostly on PH-LHD in a population with high prevalence of ischaemic heart disease. This precludes the generalisability of our findings to developing countries where aetiologies of LHDs are less of ischaemic origin and are more dominated by systemic hypertension, dilated cardiomyopathies and RHD in a younger population.[56] Therefore, PH-LHD may have a different prognosis in developing countries. Second, studies included in this review were defined PH based either on DE or RHC. RHC remains the gold standard to diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear excessive risks and be impractical in resource-limited settings. DE on the other hand is widely available, safe and relatively cheap for diagnosing PH, although the reproducibility of the approach in some circumstances has been questioned. However, a systematic review on the diagnostic accuracy of DE in PH by Janda et al[57] has shown that the correlation of pulmonary artery systolic pressure by DE compared to RHC was good with a pooled correlation coefficient of 0.70 (95% CI 0.67 to 0.73). However, studies to date examining the prognostic impact of PH in LHD have been performed in heterogeneous populations, using variable definitions of PH based both on RHC and echocardiography parameters, thus limiting any possibility of pooling. Finally, readmissions were not frequently reported and multivariable analysis when performed was characterised by a great heterogeneity in the number and range of candidate predictors included in the models, thus limiting interpretation and generalisability. Therefore, findings on these other prognostic factors must be interpreted with caution. For studies that performed only univariate analysis, we cannot rule out the possibility that the reported factors may not preserve a significant association with the outcome once adjusted for the effect of other extraneous factors. In spite of these limitations, the majority of studies included were recent and all reported on the relation of PH-LHD with all-cause mortality, making the conclusions on this relation appropriate for contemporary Western populations.

Strengths and limitations of the review

First, by restricting our search strategy to full-report articles published in English and French, and in journals available in the used electronic databases, we cannot rule out the possibility of language or publication bias. Second, we used the QUIPS instrument, designed for prognosis studies, to address common sources of bias. The QUIPS, however, lacks discriminative power; we addressed this by using the scoring algorithm suggested by de Jonge et al.[6] This scoring algorithm can still be subject to criticisms, especially because the cut-off points used to determine the quality of the studies are quite arbitrary. Third, because of important heterogeneity in the included studies, we were not able to pool data to perform a meta-analysis or to stratify data by clinically important subgroups (such as mild, moderate or severe PH). However, to the best of our knowledge, this is the

first systematic review on determinants of hospitalisations and mortality in patients with PH-LHD, and the search strategy used allowed us to present the results of several recent and high-quality publications on the topic.

CONCLUSION

The majority of studies included in this review showed that PH is an independent predictor of mortality in patients with LHD, with the more consistent evidence being in those with HF and MR. Information on readmission for heart failure was somehow very limited. The majority of this information derives from studies in Western and developed countries, and may not apply to populations in other settings. All together, these findings suggest that the hypothesis of targeting PH to improve the outcomes of patients with LHD s should be actively investigated.

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REFERENCES

1. Fang JC, DeMarco T, Givertz MM, et al. World Health Organization Pulmonary Hypertension group 2: pulmonary hypertension due to left heart disease in the adult—a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2012;31:913–33.
2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62 (25 Suppl):D34–41.
3. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012;126:975–90.
4. Haddad F, Kudelko K, Mercier O, et al. Pulmonary hypertension associated with left heart disease: characteristics, emerging concepts, and treatment strategies. Prog Cardiovasc Dis 2011;54:154–67.
5. Segers VF, Brutsaert DL, De Keulenaer GW. Pulmonary hypertension and right heart failure in heart failure with preserved left ventricular ejection fraction: pathophysiology and natural history. Curr Opin Cardiol 2012;27:273–80.
6. Vachiery JL, Adir Y, Barbera JA, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013;62(25 Suppl):D100–8.
7. Parker MW, Mittleman MA, Waksmonski CA, et al. Pulmonary hypertension and long-term mortality in aortic and mitral regurgitation. Am J Med 2010;123:1043–8.
8. Adhyapak SM. Effect of right ventricular function and pulmonary pressures on heart failure prognosis. Prev Cardiol 2010;13:72–7.
9. Merlos P, Nunez J, Sanchis J, et al. Echocardiographic estimation of pulmonary arterial systolic pressure in acute heart failure. Prognostic implications. Eur J Intern Med 2013;24:562–7.
10. Agarwal R, Shah SJ, Foreman AJ, et al. Risk assessment in pulmonary hypertension associated with heart failure and preserved ejection fraction. J Heart Lung Transplant 2012;31:467–77.
11. Agarwal R. Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. Nephrol Dial Transplant 2012;27:3908–14.
12. Aronson D, Eitan A, Dragu R, et al. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. Circ Heart Fail 2011;4:644–50.
13. Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure: a community study. J Am Coll Cardiol 2012;59:222–31.
14. Strange G, Playford D, Stewart S, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart 2012;98:1805–11.
15. Mutlak D, Aronson D, Carasso S, et al. Frequency, determinants and outcome of pulmonary hypertension in patients with aortic valve stenosis. Am J Med Sci 2012;343:397–401.
16. Tatebe S, Fukumoto Y, Sugimura K, et al. Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease. Circ J 2012;76:1235–44.
17. Stern J, Heist EK, Murray L, et al. Elevated estimated pulmonary artery systolic pressure is associated with an adverse clinical outcome in patients receiving cardiac resynchronization therapy. Pacing Clin Electrophysiol 2007;30:603–7.
18. Lee WT, Peacock AJ, Johnson MK. The role of per cent predicted 6-min walk distance in pulmonary arterial hypertension. Eur Respir J 2010;36:1294–301.
19. Moller JE, Hillis GS, Oh JK, et al. Prognostic importance of secondary pulmonary hypertension after acute myocardial infarction. Am J Cardiol 2005;96:199–203.
20. Cappola TP, Felker GM, Kao WH, et al. Pulmonary hypertension and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. Circulation 2002;105:1663–8.
21. Szwejkowski BR, Elder DH, Shearer F, et al. Pulmonary hypertension predicts all-cause mortality in patients with heart failure: a retrospective cohort study. Eur J Heart Fail 2012;14:162–7.
22. Abramson SV, Burke JF, Kelly JJ Jr, et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116:888–95.
23. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007;99:1146–50.
24. Shalaby A, Voigt A, El-Saed A, et al. Usefulness of Pulmonary Artery Pressure by Echocardiography to Predict Outcome in Patients Receiving Cardiac Resynchronization Therapy Heart Failure. Am J Cardiol 2008;101:238–41.
25. Damy T, Goode KM, Kallvikbacka-Bennett A, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. Eur Heart J 2010;31:2280–90.
26. Ristow B, Ali S, Ren X, et al. Elevated pulmonary artery pressure by Doppler echocardiography predicts hospitalization for heart failure and mortality in ambulatory stable coronary artery disease: the Heart and Soul Study. J Am Coll Cardiol 2007;49:43–9.
27. Grigioni F, Potena L, Galie N, et al. Prognostic implications of serial assessments of pulmonary hypertension in severe chronic heart failure. J Heart Lung Transplant 2006;25:1241–6.
28. Levine TB, Levine AB, Goldberg D, et al. Impact of medical therapy on pulmonary hypertension in patients with congestive heart failure awaiting cardiac transplantation. Am J Cardiol 1996;78:440–3.
29. Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–26.

30. Khush KK, Tasissa G, Butler J, et al. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: Analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. Am Heart J 2009;157:1026–34.
31. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183–8.
32. Wang D, Han Y, Zang H, et al. Prognostic effects of pulmonary hypertension in patients undergoing cardiac resynchronization therapy. J Thorac Dis 2010;2:71–5.
33. Ghio S, Temporelli PL, Klersy C, et al. Prognostic relevance of a non-invasive evaluation of right ventricular function and pulmonary artery pressure in patients with chronic heart failure. Eur J Heart Fail 2013;15:408–14.
34. Naidoo DP, Mitha AS, Vythilingum S, et al. Pulmonary hypertension in aortic regurgitation: early surgical outcome. Q J Med 1991;80:589–95.
35. Fawzy ME, Hassan W, Stefadouros M, et al. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotomy. J Heart Valve Dis 2004;13:942–7; discussion 47–8.
36. Roselli EE, Abdel Azim A, Houghtaling PL, et al. Pulmonary hypertension is associated with worse early and late outcomes after aortic valve replacement: implications for transcatheter aortic valve replacement. J Thorac Cardiovasc Surg 2012;144:1067–74 e2.
37. Melby SJ, Moon MR, Lindman BR, et al. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. J Thorac Cardiovasc Surg 2011;141:1424–30.
38. Le Tourneau T, Richardson M, Juthier F, et al. Echocardiography predictors and prognostic value of pulmonary artery systolic pressure in chronic organic mitral regurgitation. Heart 2010;96:1311–17.
39. Kainuma S, Taniguchi K, Toda K, et al. Pulmonary hypertension predicts adverse cardiac events after restrictive mitral annuloplasty for severe functional mitral regurgitation. J Thorac Cardiovasc Surg 2011;142:783–92.
40. Barbieri A, Bursi F, Grigioni F, et al. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. Eur Heart J 2011;32:751–9.
41. Manners JM, Monro JL, Ross JK. Pulmonary hypertension in mitral valve disease: 56 surgical patients reviewed. Thorax 1977;32:691–6.
42. Malouf JF, Enriquez-Sarano M, Pellikka PA, et al. Severe pulmonary hypertension in patients with severe aortic valve stenosis: clinical profile and prognostic implications. J Am Coll Cardiol 2002;40:789–95.
43. Khandhar S, Varadarajan P, Turk R, et al. Survival benefit of aortic valve replacement in patients with severe aortic regurgitation and pulmonary hypertension. Ann Thorac Surg 2009;88:752–6.
44. Zuern CS, Eick C, Rizas K, et al. Prognostic value of mild-to-moderate pulmonary hypertension in patients with severe aortic valve stenosis undergoing aortic valve replacement. Clin Res Cardiol 2012;101:81–8.
45. Ben-Dor I, Goldstein SA, Pichard AD, et al. Clinical profile, prognostic implication, and response to treatment of pulmonary hypertension in patients with severe aortic stenosis. Am J Cardiol
46. 2011;107:1046–51.
Yang C, Li D, Mennett R, et al. The impact of pulmonary hypertension on outcomes of patients with low left ventricular ejection fraction: a propensity analysis. J Heart Valve Dis
47. 2012;21:767–73.
Nozohoor S, Hyllen S, Meurling C, et al. Prognostic value of pulmonary hypertension in patients undergoing surgery for degenerative mitral valve disease with leaflet prolapse. J Card Surg
48. 2012;27:668–75.
Ward C, Hancock BW. Extreme pulmonary hypertension caused by mitral valve disease. Natural history and results of surgery. Br Heart
49. J 1975;37:74–8.
Ghoreishi M, Evans CF, DeFilippi CR, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery.
50. J Thorac Cardiovasc Surg 2011;142:1439–52.
Cam A, Goel SS, Agarwal S, et al. Prognostic implications of pulmonary hypertension in patients with severe aortic stenosis.
51. J Thorac Cardiovasc Surg 2011;142:800–8.
Pai RG, Varadarajan P, Kapoor N, et al. Aortic valve replacement improves survival in severe aortic stenosis associated with severe
52. pulmonary hypertension. Ann Thorac Surg 2007;84:80–5.
Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med
53. 2006;144:427–37.
de Jonge RC, van Furth AM, Wassenaar M, et al. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. BMC Infect Dis
54. 2010;10:232.
Vahanian A, Alfieri O, Andreotti F, et al. [Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)]. G Ital Cardiol
55. (Rome) 2013;14:167–214.
Goldstone AB, Chikwe J, Pinney SP, et al. Incidence, epidemiology, and prognosis of residual pulmonary hypertension after mitral valve repair for degenerative mitral regurgitation. Am J Cardiol
56. 2011;107:755–60.
Damasceno A, Mayosi BM, Sani M, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries.
57. Arch Intern Med 2012;172:1386–94.
Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review

1.6. Current treatment options for patients with pulmonary hypertension due to left heart disease

Overall, treatment options for patients with PH differ according to PH classification, etiologies and severity. Treatment options can be divided into two steps:

1) Primary therapy;
2) Advanced therapy.

Primary therapy refers to any treatment that is directed at the underlying cause of the PH, and is therefore warranted in nearly all patients with PH. Advanced therapy is directed at the PH itself. Five medication classes targeting PH have been evaluated in different groups of PH and are listed in advanced therapy. These include: prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulants and some calcium channel blockers. In the paragraphs below, we briefly discuss the use of these medications in PH-LHD.

1.6.1. Primary therapy for PH-LHD

The goal of primary therapy of PH-LHD is to improve global management of the underlying condition (HF due to reduced ejection fraction, HF due to preserved ejection fraction or valvular heart disease) before considering advanced therapy of specific measures to treat PH.

In HFrEF, there is strong evidence for aggressive therapy including medications for HF, cardiac resynchronization therapy of use of left ventricular assist device (31, 54). Likewise, in patients with valvular heart disease, a repair is absolutely recommended (88). In contrast, there is less strong evidence for treatment of HFpEF in general and for strategies to improve PH and outcomes in patients with HFpEF (54).

1.6.2. Advanced therapy for PH-LHD

Advanced therapy for PH-LHD is supported by its adverse outcomes and the rationale that in some patients, PH-LHD progresses from the passive and reversible post capillary PH to a

mixed and irreversible component with pulmonary arterial remodeling (86). This has justified the implementation of studies using prostanoids, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors. In Table 11 below, we summarize these studies. Overall, two major observations are worth noting:

1) Methodological limitations: These include the small sample and single-center nature of the trials, a variation in the inclusion criteria including the absence of requirement of a preliminary optimization of volume status and a variation in the stratification of patients with some based on PH and others on HF without consideration for pulmonary pressures.

2) Controversial results on the primary endpoint with two trials that suggested an improvement (101, 102), four others suggested an absence of effect (103-106) and two trials showed a negative effect (107, 108).

In summary, all trials using medications targeting PH or approved for PAH failed to demonstrate a benefit in the context of HF. Current available evidence does not therefore provide enough support for use of these drugs in clinical management of patients with PH-LHD. This results in an absence of a validated evidence based approach for advance treatment of PH-LHD. New trials are warranted to advance the field of PH-LHD.

Table 11: Completed Randomized Controls Trials using pulmonary hypertension-targeted medications in patients with pulmonary hypertension due to heart failure (modified from Vachiery et al (109)

Drug/Author Primary	Study Acronym	Patients	Design	Primary Endpoint	Results
Prostanoids : Epoprosterenol					
Califf 1996 (108)	FIRST	n=471, severe HF	1:1 randomization Even-driven, 4ng/kg/min	Survival	Early termination (trend to decreased
Endothelin receptor antagonist : Bosentan					
Bosentan Packer 2005 (107)	REACH-1	n=174, severe HF	2:1 randomization 26 week duration, 500 mg bid	Change in clinical state	Early termination (drug induced fluid retention in treated group)
Kalra, 2002 (103)	ENABLE	n=1613, HF	1:1 randomization 18 month duration, 125 mg bid	Mortality + hospital days	No effect
Endothelin receptor antagonist : Darusentan					
Lüscher, 2002(102)	HEAT	n=179 NYHA III	3:1 randomization 3-week duration, dose 30, 100, 300 mg	Hemodynamic (changes in PAWP/cardiac output)	Increased cardiac output No change in PAWP
Anand, 2004 (104)	EARTH	n=642, NYHA II-IV	3:1 randomization 6-month duration, dose 10, 25, 50, 100, 300 mg	LV changes by MRY clinical events	No effect
Phosphodiesterase 5 inhibitor: Sildenafil					
Guazzi, 2011 (101)	None	n=44, HFpEF	1:1 randomization 50 mg bid, 12-month duration	Change in mPAP	Reduction in mPAP
Redfield, 2013 (105)	RELAX	n=216, HFpEF	1:1 randomization 20 tid 12 weeks, then 60 mg tid, 12-weeks	change in exercise capacity or clinical status	No improvement
Soluble guanylate cyclase stimulator: Riociguat					
Bonderman, 2013(106)	None	n=201	4:1 randomization Riociguat 0.5, 1, or 2 mg tid for 16 weeks	Change in mPAP	No improvement

ENABLE, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure trial; Flolan, International Randomized Survival Trial; HF, heart failure; HFpEF; HEAT, Heart failure ET(A) Receptor blockade Trial; HF with preserved ejection fraction (EF); HFrEF, HF with reduced EF; LV left ventricular; MRI magnetic resonance imaging; NYHA New York Heart Association functional class; PAWP pulmonary artery wedge pressure; REACH 1, Research on Endothelin Antagonism in Chronic Heart Failure trial; RELAX, RasE-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure trial.

1.7. Knowledge gaps and implications for Africa

The review presented in this chapter has provided a contemporary synopsis of PH with emphasis on its major etiology; PH-LHD. Since the first descriptions of PH at the end of the 19th century (4), our understanding of the etiological risk factors of the disease, its diagnostic strategy and classification has improved considerably, leading to new effective therapies for at least for some forms of PH. However, PH remains a life-threatening condition if untreated, the time interval between the onset of symptoms and eventual diagnosis is still unacceptably long, up to 27 months (69) and several unanswered questions remain.

Available evidence derived essentially from specific registries of PAH in high income countries and mainly from the European or USA perspective. The systematic review presented in section 1.5 showed that PH-LHD is the most common group of diagnosed PH, even though it has to date received very little attention when compared to the abundant literature on PAH. It shall be noted that only one out of forty five articles included in this review was from an African setting. The worldwide epidemiology of PH as a whole is yet to be fully characterized and African data may differ.

Indeed, it is estimated that almost 98% of the global PH burden occurs in low income countries with a population of up to 64 million people at risk but who are undiagnosed. The epidemiology of PH in Africa and the distribution of its multitude of etiologies has not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region(110). Many known risk factors for PH are hyperendemic in this part of the world, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary hemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary diseases, PH and, often, to right heart failure (HF) with premature death(110). Also a lack of specialist pediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH(111). Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the

latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH(112). Lastly, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive right HF (110, 113). We are not aware of any registry of PH in Africa and data is scanty at best.

In the next chapter, we present the hypothesis, aims and specific questions investigated in this doctoral research.

Chapter 2. Hypothesis, Aims and specific questions

2.1. Hypothesis

We hypothesized that PH-LHD is the common cause of PH in SSA, and affected patients present with advanced disease, and ECG may have a diagnostic and/or prognostic role in screening for PH risk in this setting.

2.2. Aims

The primary aim to be achieved in this doctoral research project was to investigate the determinants and short-term outcomes of PH-LHD in the sub-Saharan African (SSA) context as well as the diagnostic utility of the widely used diagnostic tool versus echocardiography considered as the reference diagnostic test for PH in limited settings.

2.3. Specific research questions

Our specific research questions were:

1. What are the established predictors of major outcomes of PH-LHD including hospitalizations for heart failure and mortality reported in currently existing literature?

2. What are the different types of PH, clinical characteristics and 6-month outcome of patients with pulmonary hypertension in sub-Saharan Africa?

3. What are the determinants of pulmonary pressures, clinical profile and short term outcomes in patients with PH-LHD?

4. What is the prevalence and predictive utility of a simple, available and cheap tool like of electrocardiogram (ECG) for diagnosis of PH?

5. What is the prognostic significance of ECG for mortality risk in patients with acute heart failure, one of the major contributor to the etiology of PH-LHD?

Through systematic literature reviews, we have answered the first question, identifying pulmonary hypertension due to left heart disease as the most prevalent cause of pulmonary hypertension, and investigating established determinant of PH-LHD and related outcomes. We have subsequently investigated questions 2 to 4 in a cohort of PH patients from a number of countries across Sub-Saharan Africa. We have to this end investigated the effects of a range of environmental and phenotypic factors including among others, level of education, income, functional class, six minutes' walk test, echocardiographic parameters and NT-pro BNP on the presence and profile of patients with PH-LHD, as well as 6-month prognosis of the condition. Question 5 was answered through a large multicenter cohort of Sub-Saharan African patients with heart failure. The next chapter described the methods of the two major prospective multicentric cohort studies used to answer these questions.

Chapter 3. OVERVIEW OF STUDY METHODS

3.1. Introduction

Analyses presented in this thesis used data derived from two major cohort studies conducted in Sub-Saharan Africa (SSA) using similar methodological approaches. The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a clinical registry of the etiology, treatment and outcome of acute heart failure in 1006 Africans from 9 SSA countries. The Pan African Pulmonary hypertension cohort study (PAPUCO) was a multinational and multicentre clinical registry of pulmonary hypertension across 04 SSA countries.

An overview of the design of each of the two studies analysed in this thesis is presented here; more details relating to the methods of specific publications are provided in relevant chapters.

3.2. The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF)

3.2.1. Rationale and objectives

Over the past few decades, heart failure (HF) has emerged as a worldwide epidemic and an established cause of morbidity and mortality in high income countries, imposing a huge burden on their health care systems. Indeed, in some European countries and the U.S, up to 1% of the health budget is spent on the management of HF (114). Before the THESUS-HF, there was very little data on HF in Africa where most of the published data originated from single centre hospital based study and were conducted in the pre-echocardiographic era (115). It is in this context that, following a call for action (116), the THESUS-HF was established in 2007 with the aim of providing reliable evidence regarding the contemporary etiology, treatment and outcome of HF in the SSA region, through a prospective cohort study.

3.2.2. Participating centers

THE Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a prospective, multicentre, international observational survey conducted in 12 cardiology centers from 9 countries in the southern, eastern, central, and western regions of SSA (Figure 5). The countries and participating centers were selected on the basis of availability of a trained physician in clinical cardiology and echocardiography, and previous participation in research projects. The study was coordinated at Momentum Research Inc., Durham, North Carolina, USA where all data were transferred, processed, cleaned and centrally analysed. All participating centers obtained an ethical approval before joining the study.

3.2.3. Inclusion criteria

Between July 2007 and June 2011, all patients admitted with dyspnea as the main complaint in each of the participating centers, were consecutively screened for inclusion in the study. Kenya, Ethiopia and Senegal joined the study late and therefore recruited fewer patients (Figure 5). Patients were included if they were 12 years of age or older and had physical signs of congestive heart failure (i.e., pedal oedema, raised jugular venous pressure, pulmonary congestion, and tender hepatomegaly).

3.2.4. Exclusion criteria

Exclusion criteria were:

- acute ST segment elevated myocardial infarction;
- severe known renal failure (patients on dialysis or creatinine> 4 mg/dL);
- nephrotic syndrome, or hepatic failure or other cause of hypoalbuminemia;
- refusal to provide informed consent.

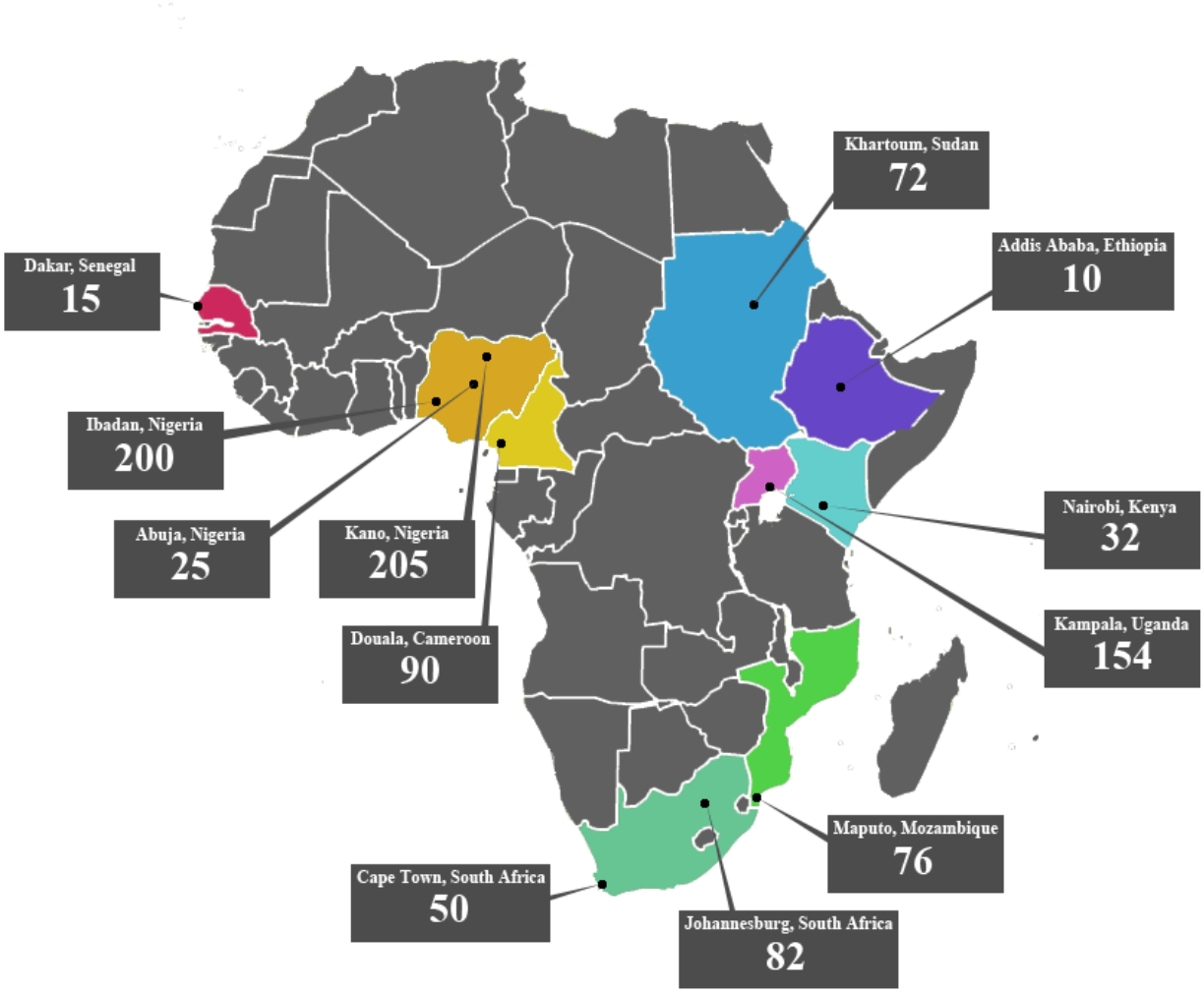

Figure 5: Patients included in THESUS-HF per country, analyses at the data lock

3.2.5. Baseline evaluation

Ethical approval was obtained from the local Ethics Committee of the participating institutions and the study conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from each eligible participant before inclusion. In total, study participants consisted of 1006 patients recruited across 12 cardiovascular centers of the nine above named countries.

3.2.6. Study visit 1

At the time of admission, demographic information was collected (patients' initials, date of birth, age, sex, area of residence, level of education) with detailed medical history, which included preadmission history of heart failure (number of acute heart failure admissions in the last year prior to index admission, date of last admission for HF and New York Heart Association (NYHA) classification one month prior to admission). An echocardiographic assessment of ventricular function, valvular structure and function and regional wall abnormalities was performed. All echocardiographic procedures were undertaken by trained physicians and measurements made according to the American Society of Echocardiography Guidelines (39). For all patients in whom a 12-leads electrocardiogram (ECG) was recorded irrespective of the date and time of recording, ECG tracings were scanned and read centrally for conduction or rhythm disturbances and for evidence of myocardial ischemia/infarction or hypertrophy. Laboratory evaluations provided by the local institution and intravenous and oral medications were recorded at admission. Baseline characteristics of the 1006 patients recruited in the THESUS-HF are presented in Table 12 for demographic and clinical and biological variables.

Table 12: Demographic, clinical and biological characteristics of the 1006 patients included in the THESUS-HF registry

Characteristic	All (N=1006)	Men (N=494)	Women (N=511)	p-value
Age, years	52.3 (18.3)	54.0 (16.9)	50.7 (19.5)	0.004
Number of AHF admissions in last 12 months	0.37 (0.78)	0.41 (0.77)	0.34 (0.78)	0.152
Number with hyperlipidaemia*	90 (9.2)	52 (10.8)	38 (7.6)	0.085
Number with a history of smoking, %	98 (9.8)	85 (17.3)	13 (2.6)	<.0001
Number with a history of hypertension, %	556 (55.5)	296 (60.0)	259 (51.0)	0.004
Number with a history of diabetes mellitus, %	114 (11.4)	58 (11.8)	56 (11.0)	0.679
Body mass index, kg/m^2	25.2 (9.0)	24.7 (4.9)	25.7 (11.6)	0.082
Systolic blood pressure, mmHg	130.4 (33.5)	132.4 (33.7)	128.4 (33.3)	0.061
Diastolic blood pressure, mmHg	84.3 (20.9)	85.5 (21.2)	83.2 (20.7)	0.084
Heart rate, bpm	103.7 (21.6)	101.6 (21.4)	105.7 (21.6)	0.002
Left ventricular ejection fraction, %	39.5 (16.5)	37.8 (16.2)	41.1 (16.6)	0.002
Creatinine, mg/dL	1.44 (1.19)	1.57 (1.21)	1.30 (1.16)	0.0004
Sodium, mmol/L	135.1 (6.6)	134.9 (6.5)	135.3 (6.8)	0.3294
eGFR< 30 mL/min/1.73 m2	73 (7.7%)	35 (7.5%)	38 (7.8%)	0.8290
Haemoglobin, g/dL	12.2 (2.6)	12.6 (2.6)	11.8 (2.5)	<.0001
Haemoglobin< 10 g/dL	147 (15.2%)	68 (14.3%)	79 (16.1%)	0.4347
Total WBC, x 109/L or 103/mm3	7699.3 (4092)	7484.1 (3505)	7914.2 (4581)	0.1032
Positive HIV serology in tested patient**	65/500 (13%)	30/240 (12.5%)	35/260 (13.5%)	0.7494

Presented are mean (SD) for continuous variables and n (%) for categorical variables. Statistics are computed from non-missing values, the number of which may vary from variable to variable. * [total cholesterol > 200 mg/dL (5.2 mmol/L), or LDL ≥ 130 mg/dL (3.37 mmol/L), or HDL < 30 mg/dL]. **Comparison of positive HIV test with Negative/Unknown

3.2.7. Ascertainment of diagnosis and follow-up

After baseline evaluation, investigators provided the diagnosis of heart failure. Cardiomyopathy was classified according to the position statement from the European Cardiac Society (117). Hypertensive heart failure, right heart failure and ischemic heart failure were defined by standard criteria.

As previously described (118), during admission, patients were systematically evaluated at days 1, 2, and 7 (or discharge whichever occurred first). Vital signs (blood pressure, heart rate, respiratory rate, and temperature), and signs and symptoms of heart failure (including oxygen saturation; degrees of edema and crackles; body weight; levels of orthopnoea) were assessed at the same time points. Changes in dyspnea and well-being relative to admission were assessed on days 1, 2, and 7 (or discharge whichever occurred first). Subjects discharged after admission were evaluated at 1 and 6 months of follow-up. At these time points patients were evaluated for signs and symptoms of heart failure, laboratory evaluations were performed, and oral medications recorded. Of the 1006 patients evaluated at baseline, 936 were reevaluated at six months. Reasons for loss to follow-up were provided for 35 of these patients and included lack of telephone contact (2.3%), financial constraints (0.3 %), unwillingness to come for follow-up (0.3%), lack of transportation (<0.1%), and others, e.g., transferring care to other facilities (0.5%).

3.2.8. Outcomes

During the follow-up period of patients discharged from the hospitals, readmissions and death, with respective reasons and cause, through 6 months follow-up were collected. A total of 159 (15.8%) patients died without completing a 6-month assessment; an additional 316 (31.4%) patients had a last date known alive provided. One-month follow-up assessments were completed for 578 (57.5%) patients and 6-month assessments for 461 (45.8%) patients.

3.2.9. Strengths

Even though THESUS-HF was an observational study, the use of a prospective and consecutive enrolment helped limiting the selection bias and acquiring a more accurate and generalizable

assessment of demographics, HF aetiologies and comorbidities as well as HF severity in the SSA region. The methodological rigor associated with standardized collection of baseline information by cardiovascular specialists and outcomes ascertainment is a major advantage as well as the large number of participants from a variety of regional ethnic groups and countries enhance the generalizability of the conclusions.

3.2.10. Weaknesses

There are some limitations to the THESUS-HF. First, in spite of the short duration of follow-up, 70 patients (7.0%) did not return for follow-up assessments for various reasons including moving to different regions of a country. This is common in the population studies due to a number of factors such as employment opportunities (migrant workers), or need to be taken care of if not well. Some of these remote regions have no phone contact. Also, although we systematically applied echocardiography and 12-lead ECG, clinical data were obtained according to the nature of the presentation and we cannot rule out the possibility of missing some cases of acute heart failure. Finally, ECGs tracings were not systematically conducted upon admission and this could limit our evaluation of ECG abnormalities during acute HF in our settings.

3.3. The PAPUCO registry

3.3.1. Rationale and objectives

Currently, available evidence on etiologies and the adverse effects of PH have been derived essentially from western clinical registries (69, 119, 120). Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared to high income countries, due to the high prevalent predisposing conditions in the region (110). The Pan African Pulmonary hypertension Cohort (PAPUCO) registry was designed and tailored to resource-constrained settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, the diagnostic and therapeutic management, and the natural course of PH in Africa. The objectives and methods of the PAPUCO, the largest contemporary cohort study of PH in Africa have been described in detail in a previous report (41).

3.3.2. Ethics

The PAPUCO study was a prospective, multicentre, international observational survey conducted in 12 cardiology centers from 4 countries (Cameroon, Nigeria, South Africa and Mozambique). Ethical approval for the study was provided by the Human Research Ethics Committee of the University of Cape Town, South Africa; the Comité National d'Ethique de la Recherche pour la Santé Humaine of Cameroon; the Comité Nacional de Bioética para a Saúde of Mosambique; the Abeokuta Health Research Ethics Committee, Nigeria; the Ethical Committee of the Aminu Kano Teaching Hospital, Nigeria, the Health Research and Ethics Committee of the Lagos University Teaching Hospital, Nigeria; the Health Research Ethics Committee of the Federal Medical Centre at the Queen Elizabeth Hospital in Umuahia, Nigeria; and the Health Review Committee of the University of Uyo Teaching Hospital, Nigeria. The PAPUCO registry complied with the revised World Medical Association Declaration of Helsinki (121, 122) and written informed consent was obtained from all participants prior to enrolment into the PAPUCO registry. The study was registered on https://clinicaltrials.gov and its identifier number is NCT02265887 (123).

3.3.3. Participating centers

Nine specialist care referral centres from Cameroon, Mozambique, Nigeria, and South Africa participated in the PAPUCO study. At the last data-lock (December 2013), 254 patients have been evaluated at baseline. Following data cleaning, 34 (13%) patients were excluded from the analysis, the remaining 220 have been included in the analysis among which 109 (50%) from the three centers in Cameroon. Because Cameroon was the largest contributor in the recruitment, the Cameroon centres is described in more detail below.

The country:

The PAPUCO Cameroon study took place in both urban and rural areas in the Central African country of Cameroon. As shown in (Figure 6) below, Cameroon is bordered by Nigeria to the west; Chad to the northeast; the Central African Republic to the east; and Equatorial Guinea, Gabon, and the Republic of the Congo to the south. Cameroon's coastline lies on the Bight of Bonny, part of the Gulf of Guinea and the Atlantic Ocean. The country hosts diverse microclimates and topographies including beaches, deserts, mountains, rainforests, and savannahs. The highest point is Mount Cameroon in the southwest, and the largest cities are Douala, Yaoundé and Garoua. Cameroon is home to over 200 different linguistic groups. French and English are the official languages.

Figure 6: Location of Cameroon and the PAPUCO-Cameroon urban centers (Douala) and the rural center (KUMBO).

According to the 2013 Human Development Report presenting Human Development Index (HDI) values and ranks for 187 countries and UN-recognized territories, Cameroon's HDI value for 2013 is 0.504. The country is characterised in a low human development category positioning the country at 152 out of 187. This is quite similar to the average HDI value of the SSA region which is the lowest of any world region (0.475), but the pace of improvement is rising. Between 2000 and 2012, the SSA region registered average annual growth of 1.34 percent in HDI value, placing it second only to South Asia. Between 1980 and 2012, Cameroon's HDI value increased from 0.373 to 0.504, an increase of 38.8 percent or average

annual increase of about 0.9 percent (124). Figure 7 below shows the contribution of each component index to Cameroon's HDI since 1980.

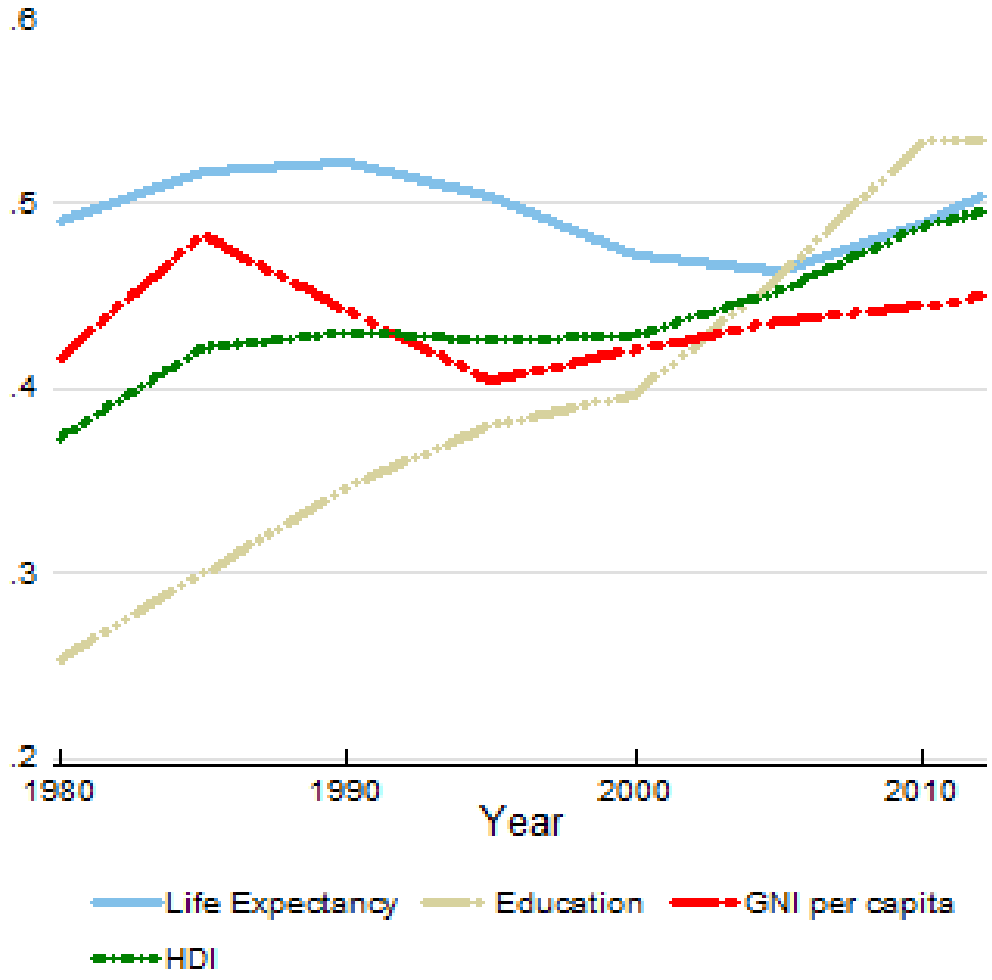

Figure 7: Trends in Cameroon's HDI component indices 1980-2012 (125)

Urban characteristics: The Douala General Hospital and Douala Cardiovascular Centre

Douala is the largest and most populated city in Cameroon with a population of approximately 2,146,844 in 2010 (126). The population of the city is heterogeneous, made up of people from all educational and professional backgrounds, all of the regions of Cameroon, immigrants and tourists. It is therefore representative of the diverse ethnicity of Cameroon. As the economic capital of Cameroon, Douala is also the largest urban center in the country.

The Douala General Hospital (DGH) is the most structured and best equipped state health care facility in Douala and receives about 25 000 (twenty five thousand) patients per annum including about 9000 (nine thousand) cases of internal medicine. Investigations for cardiac diseases in this centre include all non-invasive cardiac investigations, but cardiac catheterization is not available. An average of 500 patients undergo cardiac ultrasound each year and patients visiting DGH are usually referred from other hospitals in Douala or from other health care facilities in the country. During the study period, eight specialists trained to recognize clinical signs suggestive of PH worked at DGH including 4 cardiologists, 1 chest physician and 3 rheumatologists. Patients diagnosed with PH by other healthcare providers in Douala are likely to be referred to see these specialists for specialized management of their condition.

The Douala cardiovascular centre is the city most structured, equipped and specialized private centre with inpatients and outpatient services. During the study period, there was one full time cardiologist, 3 visiting cardiologists, and 1 visiting pulmonologist and 1 visiting rheumatologist. This centre receives up to 2000 (two thousand) patients per annum. Investigations for cardiac diseases in this centre include all non-invasive cardiac investigations. Patients visiting this centre are usually referred for cardiac care from other health facilities across Douala and beyond.

The rural area: The Shisong Cardiac Centre

Shisong, at the outskirts of Kumbo town (Figure 6), is about 400 kilometers (Km) north of Douala. It is the host of a Cardiac Centre, the Shisong Cardiac Centre (SCC), the first cardio-surgical unit in Central Africa well equipped with ultramodern technology (including cardiac catheterization and cardiac surgery) to diagnose and manage a variety of cardio surgical cases including various aetiologies of pulmonary hypertension. This centre receives about 6000 (six

thousand) patients per annum. Patients visiting the Shisong Cardiac Centre are usually from the surrounding rural areas but are also periodically referred from any health care facility in the country.

Training of the sites in Cameroon

Clinical research in SSA and Cameroon in particular is daunting due to the combined effects of several factors, including the poor training of clinicians in research, the absence of adequate infrastructure or health care system for the conduct of research, as well as funding constraints that could directly affect the conduct of the PAPUCO. To address the lack of training of clinicians and raise the interest of policy makers in clinical research, Professor Karen Sliwa, project coordinator of PAPUCO and primary supervisor of this thesis, visited the Cameroon sites for two days to provide a training seminar in research methodology with reference to the PAPUCO project, diagnosis of heart failure and pulmonary hypertension. This unprecedented event brought together three local investigators of three PAPUCO sites in Cameroon for small meetings as well as over 200 other clinicians with interest in clinical research. It was largely supported by the highest authorities of both the Douala General Hospital and the Hatter Institute of Cardiovascular Research in Africa (Figure 8). It is hoped that this first step will enhance clinical research and the dissemination of research findings to improve evidence-based clinical practice in the country (127).

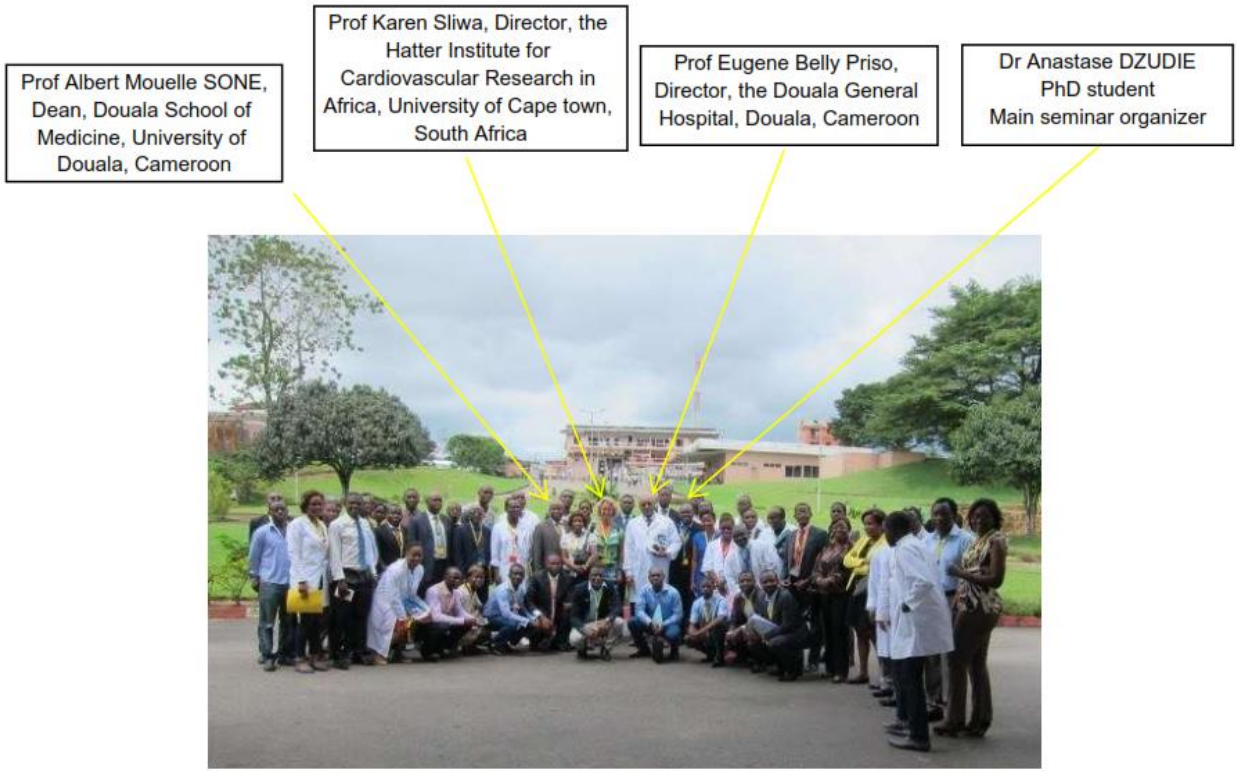

Figure 8: Official photo of the first scientific and research day held at the Douala General Hospital (128)

Other participating centers

Other participating centers included the Hatter Institute for Cardiovascular Research of the University of Cape Town, Cape Town, South Africa, the Khayelitsha District Hospital, Cape Town, South Africa, the Instituto Nacional de Saúde, Maputo, Mozambique and the department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria.

3.3.4. Inclusion and exclusion criteria

Patients were included in the PAPUCO cohort study if they were 18 years or older, and had an echocardiographic measurement of RSVP above 35 mm Hg. Patients who refused to give inform consent or who were unable to return for 6 month follow up visits were excluded.

3.3.5. Questionnaire and baseline clinical assessment

3.3.5.1. The Interview

All patients for whom an echocardiographic diagnosis of PH was made by the echocardiographer, were invited to participate. After consent, patient were then interviewed using a standardized questionnaire conceived and pretested by the PAPUCO steering committee. Information was recorded and entered onto a central research web platform (www.papuco.org) designed and conceived by integer Africa team (http://www.integerafrica.org) and pretested by the PAPUCO team during a training session of the first investigator meeting. The platform was developed with the aim of enabling investigators to track, analyse, and report on an individual-case level. The platform allowed researchers to enter data from multiple sites using one centralized database and provided tools for real-time data analysis. Using a geo-location aware data system, researchers were also able to study disease distribution and to identify risk factors. This created strong commitments and bridges for networking between centre investigators and the coordinating centre at the Hatter Institute of Cardiovascular Research in Africa, University of Cape Town. At the coordinating centre, the system was appropriately administered by integer Africa, to ensure the confidentiality, integrity and security of electronic health information. The online platform was 24-hour accessible and the architecture was developed according to clinical workflows and chronological procedures. Data was validated at the point of data entry. Multimedia data formats, i.e. electrocardiogram, chest x-rays, and echocardiography could be uploaded on the platform allowing storage of complete clinical records, which guarantees completeness of data. Tools for education, training, and communication were also installed within the web-portal. A questionnaire of the PAPUCO registry is available in the appendix section of this thesis. Briefly, the collection of information collected of:

- Demographics: Age, gender, ethnicity, occupation, educational level and income, residency, patients' contact number and that of a close relation (spouse, child).
- Clinical Variables: Family history of cardiovascular disease, presence of hypertension (defined as subject having systolic (diastolic) blood pressure of ≥ 140(90) mmHg, or physician documented history of hypertension or patient on anti-hypertensive medication), presence of diabetes (defined as past history of diabetes, or fasting blood sugar ≥ 126 mg/dL, or physician documented history of diabetes or patient on blood sugar lowering medication). Smoking status was defined as never smoked, or ex-smoker: if subject had smoked for at least 3 years in the past, but had stopped at

time of consultation, and current smoker: one who smoked at least one cigarette per day at time of consultation. Alcohol abuse was defined as intake of either more than 3 (2 for women) standard glasses of wine per day or more than 10 (5 for women) local beers (1 local beer contains 28g of alcohol) per week. Presence of symptoms (dyspnoea, fatigue, cough, palpitation) was also recorded. The World Health Organization (WHO) functional class (FC) applied (Table 13).

Table 13: World Health Organization functional assessment classification (129)

Class I:	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III:	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

- Physical examination: Jugular vein distension, presence or absence of heart murmur, hepatomegaly, ascites and pedal oedema, blood pressure (BP), pulse and respiratory rate. BP was measured using an automated electronic device with the patient in a seated position and after 10 minutes rest. Two readings were taken and the average considered.

- Anthropometric measurements: The height and weight of the subjects were measured by the clinic nurses with the participants standing, wearing indoor clothes with no shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters square. Body surface area (BSA) in meters^2 (m^2) was calculated using the formula by Dubois and Dubois:

BSA = (0.0001) x (71.84) x (weight in kg) $^{0.425}$ x (height in cm)$^{0.725}$.

- At the end of the examination, a 6 minutes' walk test (6MWT) was performed. Patient was taken to a corridor in hospital premises with already marked distance and less interference from other hospital staff or patients. The patient had to be at rest for at least 10 minutes prior to the test, during which time the procedure and importance of the test were again explained to the patient. Before walking, patient was assessed for the presence of fatigue, dyspnea and the heart rate and oxygen saturation (with pulse oximeter. Patient was then timed for six minutes and asked to walk the maximum distance within the corridor. At the end of the six minutes, patient was stopped, re-assessed for dyspnea, fatigue severity, heart rate and oxygen saturation (SpO2). The cumulative distance covered was then recorded as "6MWT distance".
- All chest X-Rays and electrocardiograms were scanned, and uploaded on the central web platform for a central analysis by the PAPUCO data management committee.
- All other tests (pulmonary function tests, Ventilation/perfusion scan, etc…) were performed at the discretion of the investigator and results were still reported on the PAPUCO web platform.

3.3.6. Echocardiographic assessment

3.3.6.1. General Assessment

The echocardiographic examination started with a general assessment during which a nurse recorded the current height and weight of the patient, the systolic and diastolic blood pressure and the heart rate at the time of the echocardiogram. If a patient presented with signs of acute pulmonary or peripheral congestion or hemodynamic instability, the exam was

postponed until hemodynamic stability achieved. Patients with acute right heart failure and no evidence of left heart disease were excluded at this stage.

3.3.6.2. Echocardiographic images acquisition and measurements

In all centers, echocardiographic and Doppler studies were performed with a 3-5 MHz sector transducer and all echocardiographic images acquisition and measurements were done according to the recommendations by the American Society of Echocardiography (ASE) (130). Hemodynamically stable subjects were positioned at 30° left lateral position (Figure 9). All echocardiographic measurements were performed by experienced cardiologist who have been trained in right heart assessment. Values were obtained directly from the screen monitor with the aid of calipers and the instrument's trackball. When heart rhythm was irregular (such as atrial fibrillation or frequent ectopic beats), each measurement was made on three consecutive cardiac cycles and an average of the three values was considered.

Figure 9: Echocardiography in a 30 years old patient positioned at 30° left lateral position

An integrated M-mode and two-dimensional study was done to determine the postero-anterior left atrial diameter (Figure 10), the septal wall thickness (SWT), posterior wall thickness (PWT), LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), consistent with the recommendations of the American Society of Echocardiography(130). Particular effort was made not to include overlying trabeculations in the ventricular septum or posterior wall measurements, which may overestimate wall thickness (Figure 11), left panel).

Ejection fraction was calculated automatically from measurements of LV diameters using the formula by Teicholz et al or estimated visually or by SIMPSON biplane method (131, 132) in case of regional wall abnormalities (Figure 11, right panel).

LV outflow tract (LVOT) diameter was measured from the systolic freeze frame of the parasternal long-axis view as the distance from where the anterior aortic leaflet cusp meets the interventricular septum to the point where the posterior leaflet meets the mitral leaflet, and perpendicularly to the anterior wall of the aortic root.

Other measurements in the left lateral position and in parasternal long axis view included aortic root diameter (Figure 10).

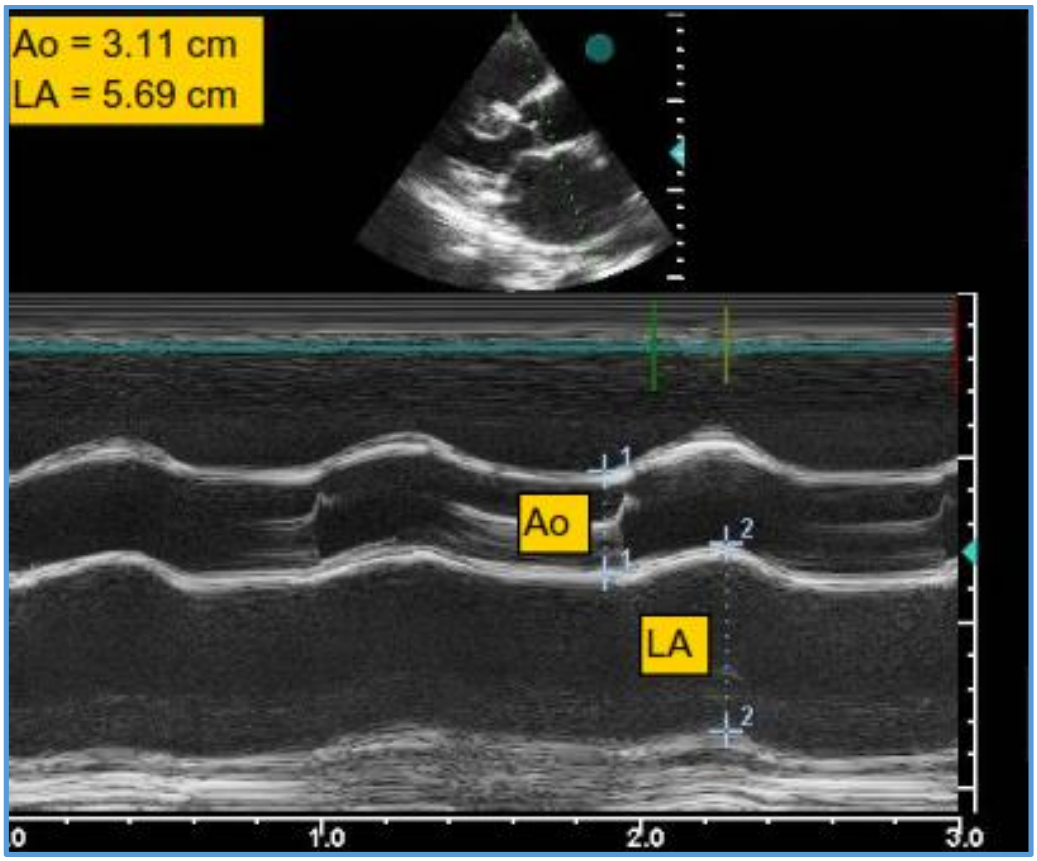

Figure 10: Echocardiographic measurements in the left lateral position and in parasternal long axis view.

Ao indicates aortic root diameter while LA indicates postero-anterior left atrial diameter.

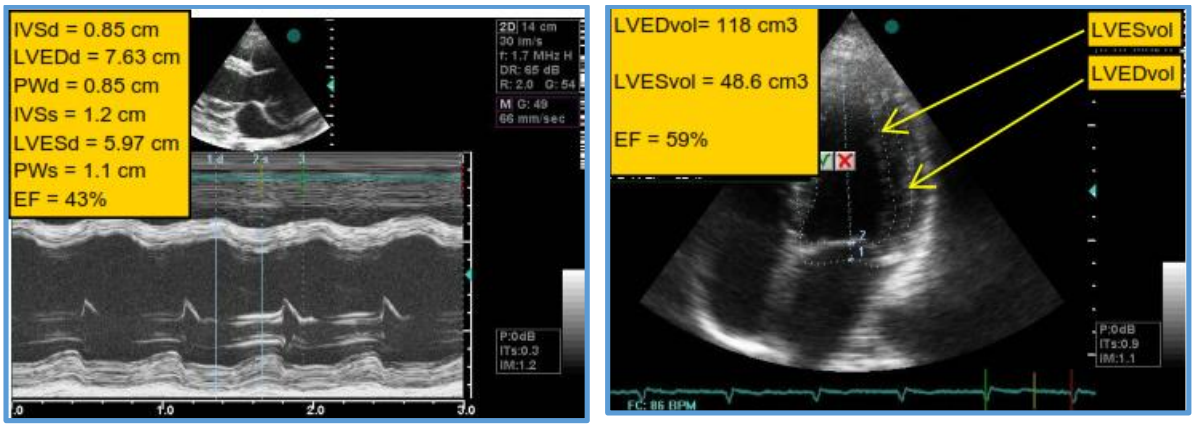

Figure 11: Measurements of the ejection fraction using the formula by Teicholz (left panel) and using by SIPMSON method (right panel).

IV(D/S) indicates Interventricular septum (diastole/systole), LVED(S)d: Left ventricular end diastolic(systolic) diameter, PWd(s): Posterior wall in diastole (systole). LVED(S)vol indicates LVED(S) volume. EF indicates ejection fraction.

We measured the LV diastolic filling velocities in an apical four-chamber view by positioning the pulsed Doppler volume sample just below the mitral annulus. Early peak flow velocity (E), late peak atrial flow velocity (A) and deceleration time (DT) were measured (Figure 12). The ratio E/A was then calculated automatically.

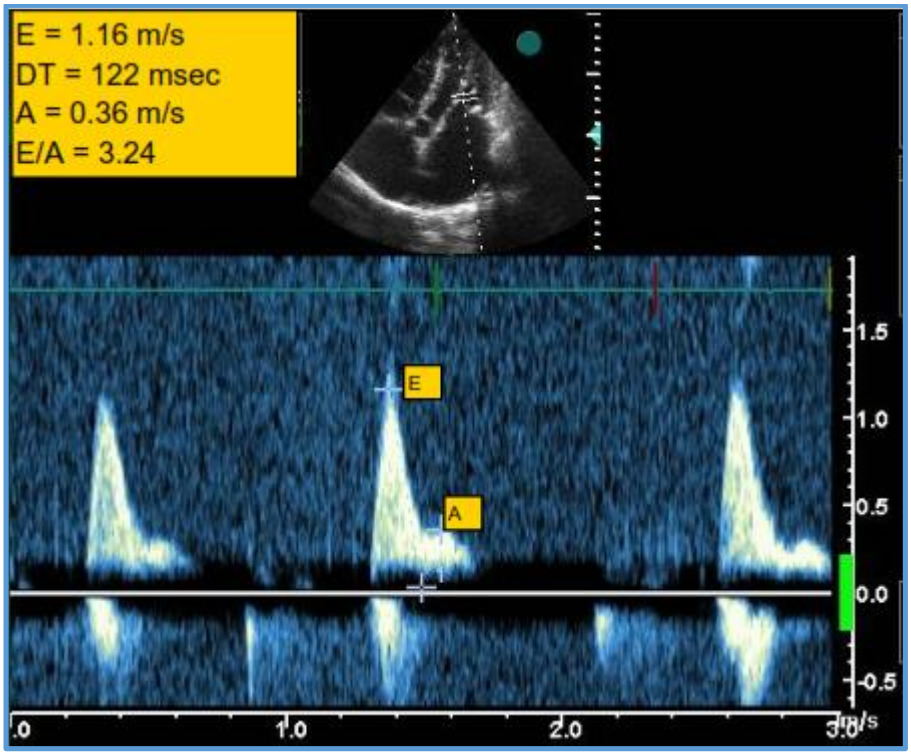

Figure 12: Measurements of LV diastolic filling velocities in an apical four-chamber view by positioning the pulsed Doppler volume sample just below the mitral annulus.

E (A) indicates early (late) peak atrial flow velocity, DT indicates deceleration time. In this patient, E/A ratio indicates a restrictive pattern of the mitral inflow.

Other parameters recorded included the aortic flow velocity, LV outflow tract time velocity integral (LVOT TVI) measured from the apical long-axis view using pulsed wave (PW) Doppler with the PW sample volume placed 3 to 5 mm below the aortic valve or at the annulus. In patients with atrial fibrillation, the average of 3 consecutive measurements from 3 consecutive cardiac cycles was considered.

Right cardiac cavities (atrial and ventricular) dilatation was diagnosed visually by the echocardiographer in four chamber apical view and classified as normal, mild, moderate, or severe dilatation (Figure 13).

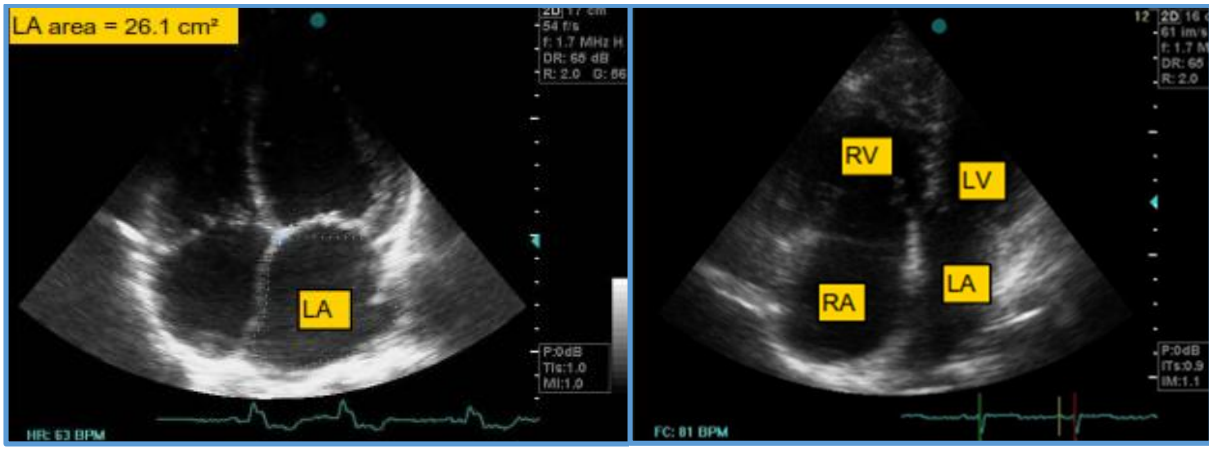

Figure 13: Visual assessment of right cardiac cavities in apical four chamber view showing mildly dilated right cavities (left panel) and severely dilated right cavities (right panel).

The assessment of RV systolic function was done visually and also using the tricuspid annular plane systolic excursion (TAPSE). TAPSE was measured as the distance of RV systolic contraction from base to apex along the longitudinal plane. To obtain this, an M-mode cursor was placed through the lateral tricuspid annulus in the 4 chamber view. The TAPSE measurement was considered as the absolute distance from systole to diastole (Figure 14). As described elsewhere (133), a TAPSE <15 mm (Figure 14) was considered as an indice of RV impaired systolic function.

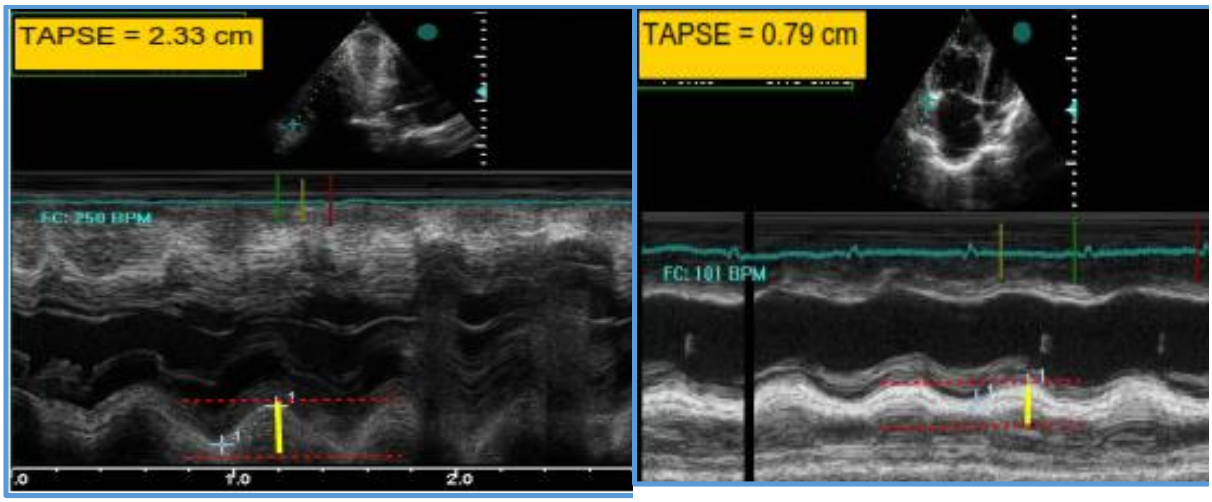

Figure 14: Measurement of the tricuspid annular plane systolic excursion (TAPSE) as indicated by the bold yellow line.

A normal TAPSE indicates a normal right ventricular (RV) systolic function (left panel) as compared to a RV impaired systolic function (right panel)

3.3.6.3. Measurement of right ventricular systolic pressure.

The RVSP was obtained by the addition of the pressure gradient between the right ventricle and the right atrium, to the pressure in the right atrium. In the absence of any significant stenosis at the right ventricular outflow tract, or the pulmonic valve, the RVSP was considered equal to systolic pulmonary artery pressure (SPAP).

To obtain the RV-RA pressure gradient, TR jet was first identified by a duplex imaging probe, in priority from the apical four chamber view (Figure 15). We then measured the maximum velocity of the tricuspid regurgitation (TR) by continuous wave (CW) spectral Doppler and the TR maximal instantaneous gradient (TR MIG) or maximum RV-RA pressure gradient was automatically calculated and listed on the screen (Figure 15). If not, TRMIG may be calculated using the Bernoulli equation as: TR MIG = 4(TR velocity)^2. TR velocity was obtained with patient's respiration held at end expiration and particular efforts were made to get a good envelope of the regurgitant jet, a necessary condition for accuracy of the measurement. We

also avoided measuring over-gained (shaggy) signals as it can significantly overestimate the RVSP.

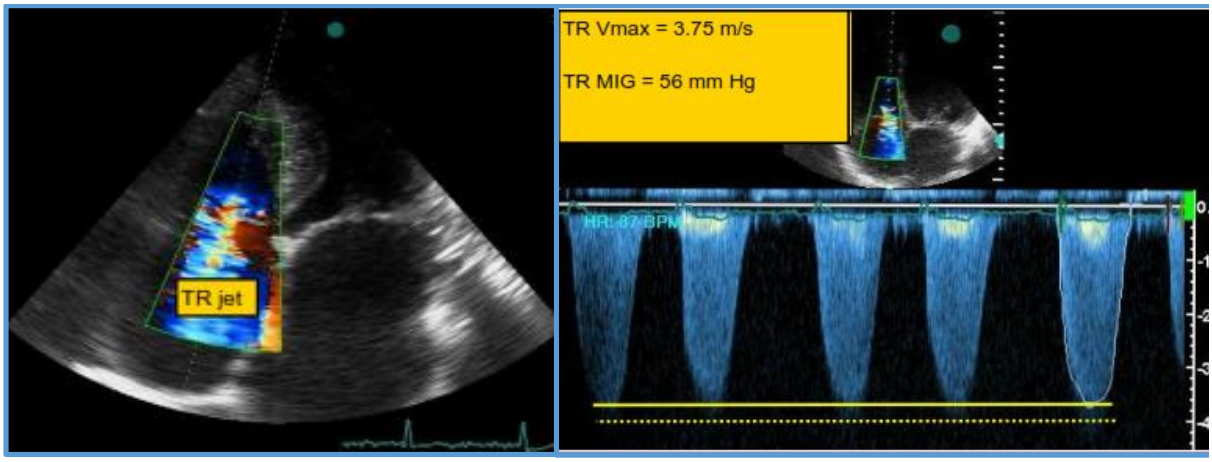

Figure 15: Measurement of the right ventricular systolic pressure

Step 1 identifying the tricuspid regurgitant (TR) jet (right panel) and step 2 using the continuous wave Doppler to obtain the maximum instantaneous right ventricular-right atrial gradient as indicated by the yellow bold line (left panel). The yellow dotted line indicates measurement of over-gained (shaggy) signals with significant overestimation in the RVSP TR jet indicates tricuspid regurgitant jet, TR MIG indicates the TR maximal instantaneous gradient. If the TR velocity signal was weak or not adequate, right ventricular inflow view, parasternal short axis view at the basal level, para-apical four chamber view or the subcostal view was then assessed and the best view considered.

3.3.6.4. Inferior vena cava assessment for estimating right atrial pressure

Right atrial pressure (RAP) was estimated from the inferior vena cava (IVC) caliber and respiratory collapsibility. With the patient lying supine, knees bent to relax the abdominal muscles, the IVC was brought into view in the long axis and measurement of the IVC diameter was made just proximal to the junction of the hepatic veins that lie approximately 0.5-3.0 cm proximal to the ostium of the right atrium (Figure 16).

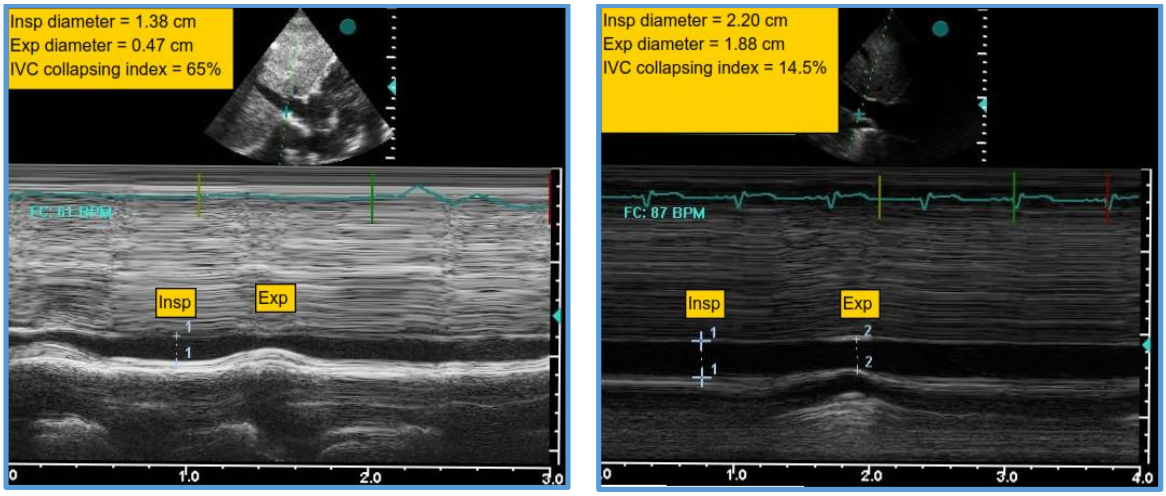

Figure 16: Estimation of the right atrial pressure from inferior vena cava (IVC) caliber and respiratory collapsibility.

The diameter of the IVC is indicated by the yellow bold line. Left panel shows a normal size IVC with estimated RAP < 5 mm Hg as opposed to the left panel showing an estimated a dilated and non-collapsing IVC with RAP > or = 20 mm Hg.

IVC diameter was measured at end-expiration (widest diameter) and end inspiration. When there was no change with inspiration, we asked the patient to sniff and measure the smallest diameter while sniffing. RAP was then estimated as described in Table 14 below:

Table 14: Estimation of the right atrial pressure from inferior vena cava caliber and respiratory collapsibility. Adapted from Beigel et al (40)

Estimated RAP (mmHg)	IVC diameter (cm)	IVC collapse with inspiration (sniff)
5	<2.1	>50%
10	<2.1	<50%
15	≥2.1	>50%
20	≥2.1	<50%

Estimated right ventricular systolic pressure (RVSP) was calculated as follows: **RVSP = TR MIG + RAP or RVSP = 4(TR velocity)² + RAP** and estimated RVSP = estimated pulmonary artery systolic pressure.

3.3.7. Measurement of NT-pro Brain Natriuretic Peptide Levels

Blood samples were taken from 65 subjects with PL-LHD from the PAPUCO Cameroon centers who gave their informed consent prior to blood extraction. At first, blood samples were collected by venipuncture into a tube containing ethylene diamine tetra acetic acid (EDTA) (1 mg/mL blood) with aprotinin (50 kallikrein inactivator units per mL of blood) and immediately centrifuge at 2,220 rpm for five minutes. The top clean serum was removed from the centrifuged tube using a pipette and taking care not to take up any of the red blood cells and 1.4 ml of serum was transferred into three barcoded tubes. Serum samples were then frozen at -20 degre C until day of transfer to the laboratory of the Hatter Institute of Cardiovascular Research in Africa (HICRA), University of Cape Town, South Africa. During transfer, samples were transported into a dry ice in a cooler box and remained frozen until arrival in the laboratory at the HICRA (Figure 17). Upon arrival in the laboratory, the frozen samples were again placed in a -80 degre C freezer until analysis were performed.

Figure 17: Blood samples upon arrival at the laboratory of the Hatter Institute of Cardiovascular Research in Africa.

Yellow tubes indicates serum samples and purple tubes indicates plasma samples.

At the HICRA, we used the enzyme immunoassay for the quantitative determination of NT-proBNP in human EDTA plasma or serum. First, all reagents and samples were kept at room

temperature (18-26°C) before use in the assay. In a first step, sample and conjugate (sheep anti-human NT-proBNP-HRPO) were pipetted into the wells of the microtiter strips (Figure 18, left panel), which were precoated with polyclonal sheep anti NT-proBNP antibody. This allowed the NT-proBNP present in the sample to bind to the precoated antibody in the well and forms a sandwich with the detection of antibody (Figure 18, right panel).

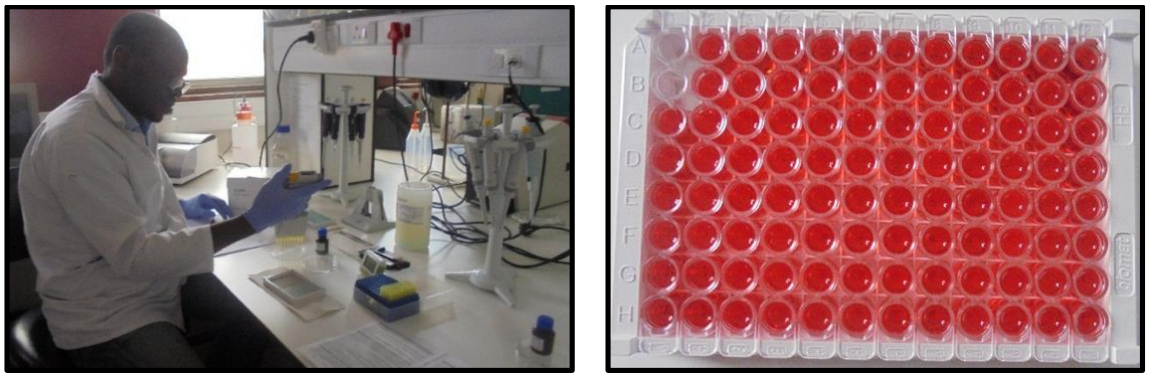

Figure 18: Pipetting the sheep anti-human NT-pro BNP-HRPO into the wells of the microtiter strips (left panel), and which results into to binding of the NT-pro BNP to the precoat and colored red (right panel).

In the washing step, using an ELISA micro plate washer, all nonspecific unbound material were removed. In a second step, the substrate (TMB Tetramethylbenzidine) was pipetted into the wells. This allowed a color change of the substrate which is directly proportional to the amount of NT-proBNP present in the sample (Figure 19).

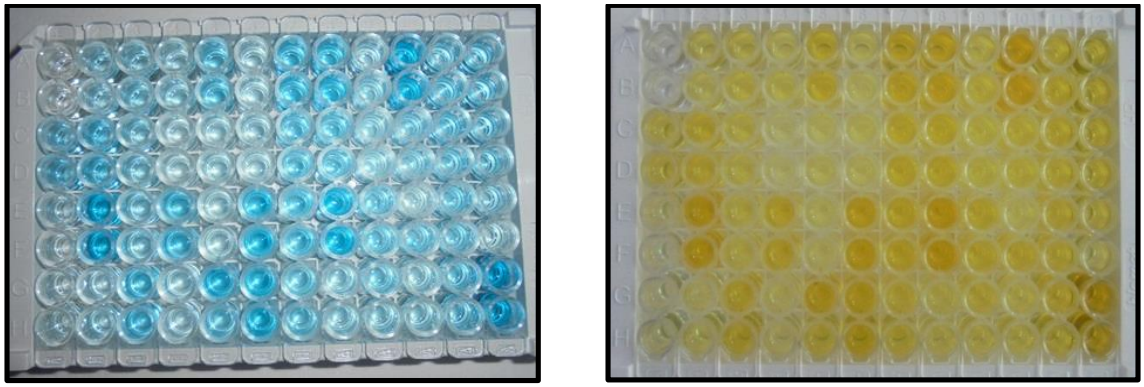

Figure 19: Color change of the substrate following pipetting of the substrate (TMB Tetramethylbenzidine) into the wells.

The color change is directly proportional to the amount of NT-proBNP present in the sample. This color change was detected with a standard microtitter plate Elisa reader. Absorbance was measured after 30 minutes at 450 nm with reference 650 nm using a spectrophotometer (Figure 20).

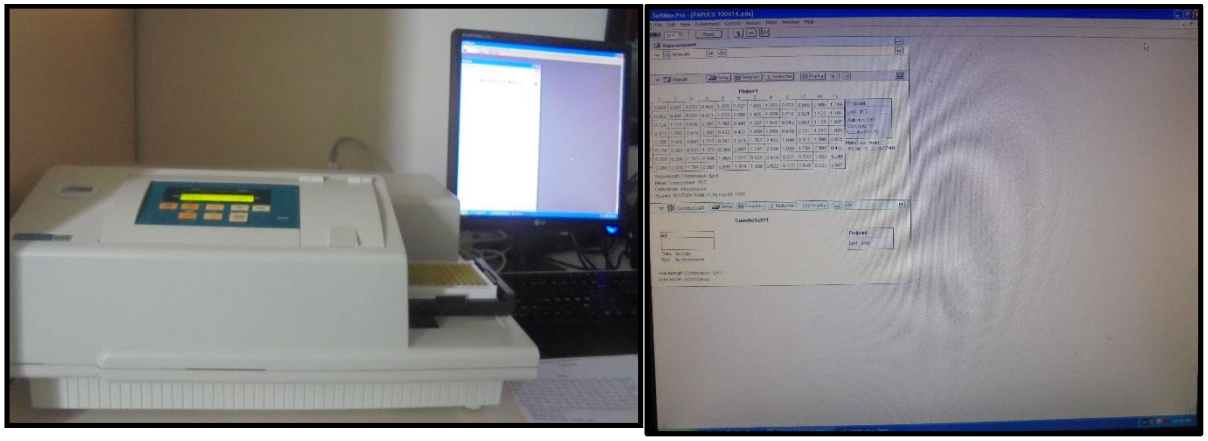

Figure 20: Measurement of optical densities using a spectrophotometer (left panel), the readings are viewed on the screen (right panel).

Calculations of NT-proBNP results from optical densities were conducted by subtracting the blank extinction from all other values and we constructed a standard curve from the standard values using the prism software. We then read the sample concentration from the constructed standard curve. Dilution factors were taken into consideration for calculation of the samples.

3.3.8. Follow up and outcomes

All patients included in the PAPUCO registry were entered into the study from the date they gave their inform consent to participate and were followed up until death or 31st December 2013 (which ever occurred first) when all patients still actively followed up were censored. For all patients, follow-up evaluations were performed by telephone interview with the patient, the patient's family, the patient's primary physician or cardiologist. The two outcomes considered were heart failure admission and all cause death within 6 months with an allowable window of 5 to 9 months from baseline. Questions asked to participants or their proxies included recent emergency room visits, hospitalizations, or death. The verbal autopsy then investigated whether 1) patient was alive on 31st December 2013. 2) if alive, we recorded number and dates of admissions, as well as time lapse from recruitment to the first admission. If the patient died, we recorded date of death and calculated time lapse from recruitment to death. Admission (all-cause mortality) was defined as any heart failure admission (all-cause death) during the follow up period of 6 months with allowable window of 5 to 9 months from baseline. Patient was considered lost to follow up if unreachable by phone after more than 15 attempts on 3 different days. The above information was documented in the PAPUCO web base platform.

3.3.9. Data cleaning, case and outcome ascertainment

The method of case ascertainment was standardized for all centers and based on the investigator report. All cases were reviewed by two investigators, Anastase Dzudie (AD) and Friedrich Thienneman (FT) to check for missing values and data consistency. In case of inconsistency, a query was addressed to the investigator and corrections were made on the patient's case report form with investigator signature below. If queries were satisfactorily addressed, and there was no inconsistency, patient's data was included in the analysis. In case of inconsistency, a discussion via Skype call with the investigator was organized and a consensus was reached.

The method of outcome ascertainment was the same across centres. Investigators questioned participants or their proxies regarding recent emergency room visits, hospitalizations, or death and entered the information on the PAPUCO web based platform. Additionally, whenever possible, admissions or deaths were always identified using hospital records, particularly for the two centers in Cape Town where outcomes could always be tracked through clinicum, the hospital record system. Again, when the outcome was imprecise or inconstant, a query was sent to the investigator and a consensus decision was only taken after failure to answer the query following a discussion via Skype call between AD, FT and the centre investigator. All disagreement between the two adjuticators (AD and FT) were resolved by consensus and if consensus was not achieved, a third opinion (Karen Sliwa (KS) or Ana Olga Mocumbi (AOM) was requested.

3.3.10. PH classification

In a first step, clinical history, physical examination, chest X-ray, ECGs, biology, echocardiography, and lung function tests, computed chest pulmonary angiography, V/Q scan (when available) for all patients were reviewed by two investigators (AD and FT) for completeness, data verification and validation of PH classification. In case of any disagreement, a query was addressed to the investigator, and if consensus on the WHO classification of PH could not be reached, a third investigator's (KS or AOM) opinion was requested. During this process, transthoracic echocardiograms were particularly reviewed to assess the cardiac morphology and function and valvular anatomy and function.

3.3.11. Study limitations

Potential methodological limitations should be acknowledged to facilitate the interpretation of our results.

1) **Validity of right ventricular systolic pressure for diagnosis of pulmonary hypertension**

First, our diagnosis of PH was echocardiographic based on RVSP measurement as the sum of TR maximal instantaneous gradient and right atrial pressure. There is absolutely no doubt that right heart catheterization (RHC) is the standard to accurately diagnose PH and determine its

severity as well as impact on right ventricular function. However, RHC is an invasive procedure, it is expensive and not always available, particularly in SSA. There is an abundant literature on the validity of echocardiographic RVSP estimates in patients with left heart disease using RHC values as the gold standard. Lanzarini et al reported(134) a concordance correlation coefficient of 0.88 between RHC and RVSP, with ±20 mm Hg 95% limits of agreement. Other studies reported a narrower limit of agreement (<10 mm Hg) and good correlation between RHC and RVSP (r=0.82–0.97) in HF (135-137). In their study of echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure, Nagueh et al (138) reported that echocardiography identified patients with invasive systolic pulmonary artery pressure >35 mm Hg with 94% sensitivity and 90% specificity. In an analysis of data from the ESCAPE trial, McClanahan and M. Guglin (139) suggested that the accuracy of echocardiographic RVSP estimates in systolic HF might be inaccurate in presence of RV systolic dysfunction. However, at least two reasons could have explained this lack of accuracy: 1) first, patients included in the ESCAPE trial (140) were in acute heart failure and not hemodynamically stable; 2) echocardiography in ESCAPE was not protocol driven, and the time differential between RHC and RVSP evaluation using echocardiography was widely variable.

As described in Chapter 1 of this thesis, Doppler echocardiography is recommended by the ESC/ERS guidelines (141) and the ACCF/AHA 2009 expert consensus as the reference screening method to detect PH in population at risk. We have also reported in Chapter One that regardless of method of PH determination (echocardiography or RHC), PH is associated with adverse outcomes. Therefore, provided that patients are hemodynamically stable and a rigorous echocardiographic technique is used by experienced observers, it is acceptable and pragmatic to detect PH using echocardiographic estimates of RVSP.

2) Sample size and follow-up

We acknowledge the short duration of follow-up (6 months) and the small number of participants included in our registry with blood samples in only 65 patients. An explanation to the sample size is that contrary to other registries which included both new and old cases, we included only newly diagnosed cases of PH. This small sample size would not allow us to have reliable information on prevalence data, but is unlikely to affect the direction of associations.

The planned PAPUCO 2 will hopefully address this shortcoming by recruiting more participants and allowing for extended follow-up.

3.3.12. Strengths of the PAPUCO registry

Strengths of this study include the prospective and consecutive nature of data collection in the real world practice of SSA by cardiovascular specialists. The web based platform provided a networking opportunity for all investigators from different countries and a standardised collection of baseline information and outcomes ascertainment. The inclusion of participants from a variety of ethnic groups and different countries enhances the generalizability of the conclusions. Also data was rigorously cleaned by reviewing each case by two investigators (Anastase Dzudie and Friedrich Thienneman) and disagreement resolved by consulting a third one (Karen Sliwa). This approach enhances its internal validity, and the non-selective nature of participants enhances the external validity. Further, we relied on rigorous validated Doppler echocardiography techniques to diagnose PH and associated LHD.

3.4. Details of rationale and design of the PAPUCO study (Second publication)

This section on the details of PAPUCO objectives and study methods has been published as a research paper in the peer-reviewed journal “BMJ Open”.

BMJ Open

Rationale and design of the Pan African Pulmonary hypertension Cohort (PAPUCO) study: implementing a contemporary registry on pulmonary hypertension in Africa

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ABSTRACT

Introduction: Pulmonary hypertension (PH) is a devastating, progressive disease with increasingly debilitating symptoms and usually shortened overall life expectancy due to a narrowing of the pulmonary vasculature and consecutive right heart failure. Little is known about PH in Africa, but limited reports suggest that PH is more prevalent in Africa compared with developed countries due to the high prevalence of risk factors in the region.

Methods and analysis: A multinational multicentre registry-type cohort study was established and tailored to resource-constraint settings to describe disease presentation, disease severity and aetiologies of PH, comorbidities, diagnostic and therapeutic management, and the natural course of PH in Africa. PH will be diagnosed by specialist cardiologists using echocardiography (right ventricular systolic pressure >35 mm Hg, absence of pulmonary stenosis and acute right heart failure), usually accompanied by shortness of breath, fatigue, peripheral oedema and other cardiovascular symptoms, ECG and chest X-ray changes in keeping with PH as per guidelines (European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines). Additional investigations such as a CT scan, a ventilation/perfusion scan or right heart catheterisation will be performed at the discretion of the treating physician. Functional tests include a 6 min walk test and the Karnofsky Performance Score. The WHO classification system for PH will be applied to describe the different aetiologies of PH. Several substudies have been implemented within the registry to investigate specific types of PH and their outcome at up to 24 months. Data will be analysed by an independent institution following a data analyse plan.

Ethics and dissemination: All local ethics committees of the participating centres approved the protocol. The data will be disseminated through peer-reviewed journals at national and international conferences and public events at local care providers.

Strengths and limitations of this study

- The Pan African Pulmonary hypertension Cohort (PAPUCO) study is the first multinational registry on pulmonary hypertension in Africa.
- PAPUCO centres have different levels of medical infrastructure and not all patients underwent the same rigorous workup.

INTRODUCTION

Pulmonary hypertension (PH) is a devastating, progressive disease with increasingly debilitating symptoms and usually shortened overall life expectancy due to a narrowing of the pulmonary vasculature and consecutive right heart failure (RHF).[1] The epidemiology of PH in Africa and the distribution of its multitude of aetiologies have not yet been described, but limited reports suggest that the incidence of PH in Africa is higher than that reported from developed countries, owing to the pattern of diseases prevalent in the region.[2–5] Many known risk factors for PH are hyperendemic in this part of the world, including HIV/AIDS, rheumatic heart disease (RHD), hereditary haemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On the other hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining may subsequently lead to various forms of pulmonary disease, PH and often to RHF with premature death. Also, a lack of specialist paediatric services to diagnose and manage congenital heart disease (CHD) potentially also leads to PH.[6] Furthermore, the high

prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH.[6–8] However, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischaemic heart diseases. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive RHF.[4 9] Thus, within the registry, we expect the entire spectrum of aetiologies of PH. In this manuscript, we aim to provide an overview of PH in Africa and the epidemiology of risk factors prevalent in the region, and answer the question why Africa needs a registry for PH just as much as most other parts of the world and how we implemented it in the setting of scarce resources.

Preliminary evidence of a significant burden of PH and its risk factors in Africa

In recent years, there has been an increasing awareness of the clinical significance of PH and cor pulmonale in Africa. This applies equally to the recognition of the importance of PH and RHF as a primary diagnosis and as a poor prognostic marker for those primarily affected by left-sided heart failure. Data on the precursors and risk factors of those conditions are limited to a few reports. The largest study on PH/RHF in Africa has been conducted within the Heart of Soweto Study in South Africa; 2505 patients presented with de novo heart failure between 2006 and 2008.[5] Of those, 697 (28%) were diagnosed with PH/RHF. PH/RHF was the primary diagnosis in 50% of those patients. The majority presented with dyspnoea and a mean right ventricular systolic pressure (RVSP) above 50 mm Hg. Left heart disease (31%), chronic lung disease due to chronic obstructive pulmonary disease and TB (26%), and pulmonary arterial hypertension (PAH; 20%) due to HIV (HIV-PAH), CHD or idiopathic PAH were the most common causes of PH. Sani et al[10] described the prevalence of PH in patients with RHD at a tertiary centre in Nigeria. Of 1312 Echocardiography (ECHO) studies, 10% had evidence of RHD; secondary PH was present in 80% of patients with RHD. The same centre reported on 53 patients with PH on ECHO among 80 patients admitted with heart failure, with hypertensive heart disease (25%), peripartum cardiomyopathy (25%), dilated cardiomyopathy (17%) and RHD (13%) being the most common causes of PH.[11] A study from Uganda showed a prevalence of PH in patients with newly diagnosed RHD (n=309) of 33%.[12] A smaller survey from Lagos, Nigeria, investigated the prevalence of cardiovascular disease in an HIV-positive cohort and found 1 patient of 100 patients to have HIV-PAH.[13] An ECHO study on 102 HIV patients presenting with cardiac symptoms in Tanzania revealed PH in 13%.[14] PH with an RVSP>30 mm Hg was present in 4% of long-term survivors in a Zimbabwe cohort of vertically acquired HIV infection.[15] Haemolytic anaemia is a known risk factor for PH; a screening study of patients with sickle-cell disease (SCD) in Nigeria showed a PH prevalence of 25%[16]; a study from Egypt indicates that patients with β-thalassaemia are at risk of PH.[17] Another study from Egypt found a PH prevalence of 9% in patients seropositive for schistosomal antibodies. Ahmed et al[18] from Sudan described 14 consecutive cases of PH with previously treated pulmonary TB and concluded that PH can even occur after resolution of TB, most likely due to persistent lung destruction. These data suggest that left heart disease, chronic lung disease, RHD, HIV, schistosomiasis and SCD might be the most common underlying diseases to cause PH within the spectrum of aetiologies of PH that we will find within the Pan African Pulmonary hypertension Cohort (PAPUCO)

RATIONALE AND OBJECTIVES

Worldwide, PH has received a great increase in awareness at the beginning of the 21st century, but less than 1% of the publications are from Africa (figure 1). It is expected that PH is more prevalent in Africa compared with developed countries, but little information is available about African patients with PH. Exposure to risk factors, human genetic variation, different socioeconomic backgrounds, lifestyles, comorbidities, nutrition and disparities in access to health services makes the African population unique but heterogeneous at the same time. Therefore, most research data and clinical guidelines from high-income countries cannot be translated into the African context. It is within the context described above that PAPUCO, a Pan Africa registry-type cohort study, was established (figure 2).

Scientific and clinical research has been fundamental in improving human health.[19] In fact, research has been demonstrated to be an excellent vehicle to implement new technologies and to facilitate training for its use, as well as to develop new systems and establish the services around it—jointly leading to technical improvement, sharpening of skills and capacity development.[20 21] Besides the main objectives of the PAPUCO registry to define and understand PH in Africa (box 1), this multinational and multicentre research project therefore aims to also develop sustainable clinical and research capacity across the African continent as well as raising awareness for PH and its risk factors.

The prevalence of PH in Africa varies geographically, according to the underlying risk factors and diseases, and the diagnosis of PH is most likely often missed, not only during the early stages due to the subtle nature of presentation of PH, but also at a more advanced stage of the disease, due to a lack of awareness by primary care doctors and low index of suspicion, limited access to ECHO services and tertiary care. However, it is crucial to diagnose PH in Africa early and reliably to ensure better care for these patients (box 2).

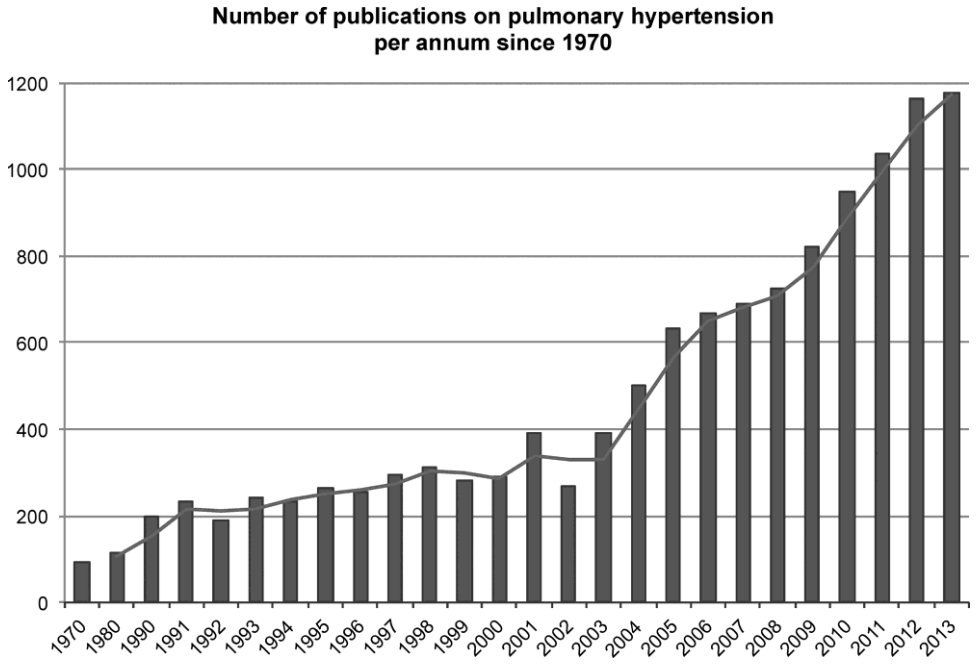

Figure 1 Number of publications on pulmonary hypertension per annum since 1970 (grey bars) with moving average (blue line). Less than 1% (0.7%) of the publications were from Africa (not displayed). Title search terms in PubMed were 'pulmonary hypertension', 'pulmonary arterial hypertension' or 'pulmonary venous hypertension' and Africa and African country names; results are displayed annually between 1970 and 2013.

METHODS AND ANALYSIS

Study design and setting

The PAPUCO research group was established in 2011 with the aim of implementing a registry-type cohort study on PH in Africa. The registry aims to recruit consecutive patients (1) with newly diagnosed PH-based clinical and ECHO criteria, (2) who are able or likely to return for a 6-month follow-up, (3) who are at least 18 years old (except for those in paediatric centres in Mozambique and Nigeria) and (4) who consented in writing to participate in the registry. Centre eligibility includes (1) availability of ECHO and training in assessing right heart function, (2) experience in diagnosing PH according to the WHO classification, (3) experience in clinical management of patients with RHF and (4) resources to review patients at 6-month follow-up. Participating centres will be invited to join the registry at African cardiac meetings and conferences.

Definition of PH, diagnostic algorithm and data points

As shown in box 3, PH is defined as documented elevated RVSP>35 mm Hg on transthoracic ECHO in the absence of pulmonary stenosis and acute RHF, usually accompanied by shortness of breath, fatigue, peripheral oedema and other cardiovascular symptoms, and possibly ECG and chest X-ray (CXR) changes in keeping with PH as per the European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines on PH.[5 22] Right heart catheterisation is optional. The updated WHO classification system for PH (Dana Point 2008) will be applied to describe the different aetiologies of PH.[22 23] Once definitive assessment and treatment has been applied, the following specific data will be documented for each individual: (A) all major cardiovascular diagnoses according to the International Classification of Diseases (ICD) 10 coding, and (B) up to five non-cardiovascular diagnoses according to ICD 10 coding.[24] Figure 3 shows the diagnostic algorithm to diagnose PH in resource-constraint settings without access to right heart catheterisation that has been developed following the ESC/ERS guidelines for the diagnosis of PH.[22] Key information collected will include information on demographic profile, socioeconomic background, medical history, comorbidities, cardiac risk factors and environmental exposures. The clinical aspects of the assessment include symptom scoring, a full clinical examination, physical and clinical status; functional tests include the WHO functional class (WHO FC), a 6 min walk test (6MWT) and the Karnofsky Performance Score. Technical procedures include ECHO, CXR and a 12-lead ECG. Further investigations are at the discretion of the treating physician and typically include lung function tests, ventilation/perfusion lung scans, high resolution CT and CT pulmonary angiography, and right heart catheterisation, if available (figure 3). Data on heart failure treatment and co-medication, hospitalisation and death, and 6-month outcome will also be collected.

Echocardiography

Echocardiography in adults

ECHO modalities applied included M-mode, two-dimensional (2D) and Doppler studies. ECHO will be

Figure 2 The Pan African Pulmonary hypertension Cohort (PAPUCO) map displays countries currently participating in the PAPUCO registry (number of centres per country in brackets).

performed with 3–5 MHz sector transducer. Complete 2D ECHO examination will be performed according to the recommendations of the American Society of ECHO (ASE).[25] M-mode ECHO will be derived from 2D images. The M-mode cursor on the 2D scan will move to specific areas of the heart to obtain measurements according to the recommendation of the committee on M-mode standardisation of the ASE. Doppler indices of left ventricular (LV) diastolic filling will be obtained. A complete Doppler study will be carried out according to the recommendations of the ASE. From the M-mode measurements, indices of LV function will be derived. These include shortening fraction, ejection fraction (EF), and LV mass, cardiac output and relative wall thickness. ECHO examinations include (A) valvular assessment, (B) left atrial size, (C) LV size and function, (D) a semiquantitative estimate of the severity of valvular regurgitation, (E) size and function of the right atrium and the right ventricle (RV; figure 4A) and (F) evidence of PH. Doppler will be used to examine the valves on suspicion of any valvular lesion. ECHO findings associated with PH include a dilated pulmonary artery and dilation and hypertrophy of the RV, diastolic flattening of the interventricular septum and Doppler evidence of PH.[26] Doppler ECHO estimates the pulmonary artery systolic pressure (PASP). By measuring the maximum

Box 1 Pan African Pulmonary hypertension Cohort (PAPUCO) objectives

Primary objective
To describe disease presentation, disease severity and aetiologies of pulmonary hypertension (PH), comorbidities, diagnostic and therapeutic management, and the natural course of PH in Africa.
Secondary objectives
To describe the overall 6-month survival rate.
To describe the 24-month survival rate in patients with HIV-pulmonary arterial hypertension.
To compare 6-month survival rates between different groups of PH.
To determine the predictors of mortality access the different groups.

Box 3 Evidence to diagnose pulmonary hypertension in resource-constraint settings

Symptoms: shortness of breath, fatigue, cough, chest pain, palpitations.
Clinical examination: raised jugular vein pressure, peripheral oedema, ascites, loud p2, systolic murmur, central cyanosis.
ECG: sinus tachycardia, p-pulmonale, right axis deviation, right bundle branch block, right ventricular hypertrophy.
Chest X-ray: cardiomegaly, pleural effusion, prominent pulmonary arteries.
Echocardiography: dilated right atrium and ventricle, interventricular septal flattening, right ventricular systolic pressure >35 mm Hg, tricuspid annular plane systolic excursion <15 mm (figure 4).

velocity of the tricuspid regurgitant jet (v, figure 4B), the transtricuspid pressure gradient will be calculated using the modified Bernoulli equation ($4v^2$).[27] The PASP is approximated by adding the transtricuspid gradient to the right atrial pressure (RAP) as applied in the formula [$PASP=4v^2+RAP$]. The PASP is equivalent to RVSP in the absence of pulmonary outflow obstruction. The RAP is estimated by the respiratory variation size of the vena cava inferior in M-mode.[28] In our study, the systolic regurgitant tricuspid flow will be assessed in the parasternal RV inflow, parasternal short-axis and apical four-chamber views to determine the highest velocity, which reflects PASP/RVSP.[29] PH is defined as mild if RVSP was 36–50 mm Hg, moderate if RVSP was 51–60 mm Hg and severe if RVSP was >60 mm Hg.[30] In addition, we further assessed RV function by measuring the systolic displacement of the lateral portion of the tricuspid annular plane excursion on the M-mode tracing under the 2D-echo guidance (figure 4C).[31] Peak mitral early diastolic velocity (E in m/s), the E-wave deceleration time (DCT in ms) and the velocity at atrial contraction (A in m/s) are measured using pulsed-wave Doppler. LV filling pressure classes were defined in accordance with the ASE 2009 guidelines.[32] In patients with heart failure and reduced EF (HFrEF), raised LV filling pressure is defined as E/A ≥2 if in sinus rhythm or DCT <150 ms if in atrial fibrillation (AF); normal LV filling pressure is defined as E/A <1 in patients in sinus rhythm or DCT ≥200 ms for those in AF; patients between these limits will be classified as undetermined. In heart failure and preserved EF (HFpEF), LV filling pressure is classified as follows: raised LV filling pressure if the left atrium is dilated and normal LV filling pressure if the left atrium is of normal size.

Box 2 The significance of pulmonary hypertension (PH) in Africa: Why we need to diagnose?

The right to know.
Prognostic implications.
Access to tertiary care: heart failure management, anticoagulation, home oxygen, chronic obstructive pulmonary disease manage- ment, access to PH-specific drugs (sildenafil).
Access to cardiothoracic surgery: valve repair/replacement, correction of congenital heart disease, heart transplantation.
Access to social and disability grants.
To raise awareness of PH and its risk factors.

Echocardiography in infants and children

Translating the definitions of PH in adults to children, especially to infants, is controversial. Within the paediatric cardiology community, experts suggest that the ratio of the PASP to the systemic systolic blood pressure >0.4 should be the diagnostic criterion.[33] The fact that the threshold of pulmonary vascular resistance (PVR) increase has not been included in the aforementioned definition is another limitation of its use in children or infants, since paediatric PH is mainly caused by left-to-right shunt CHD; and if PVR shows no significant increase in such cases, the patient may be considered only as a dynamic PH case led by increased pulmonary blood flow, rather than pulmonary vascular disease. Paediatric guidelines suggest that mPAP >25 mm Hg and PVR>3 Wood units remain in the definition of PAH.[34] In our cohort of children with congenital heart malformations, we used not only tricuspid and pulmonary regurgitation envelopes, but also the flow across the ventricular septal defect or persistent ductus arteriosus to measure the gradient between the two circulations and therefore estimate the pulmonary pressure. Indirect signs of PH, such as dilation of the RV, RV-hypertrophy and dilation of the main pulmonary artery, were added to Doppler data to confirm the diagnosis.

Accuracy of echocardiography in the diagnosis of PH

Diagnosing PH is challenging when relying on bedside tests. RHC is the gold standard to diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear excessive risks and be impractical in any cost-constrained environment. Also, RHC is only available at very few centres in Africa. A viable device to diagnose PH in Africa needs to be widely available, accurate, safe and

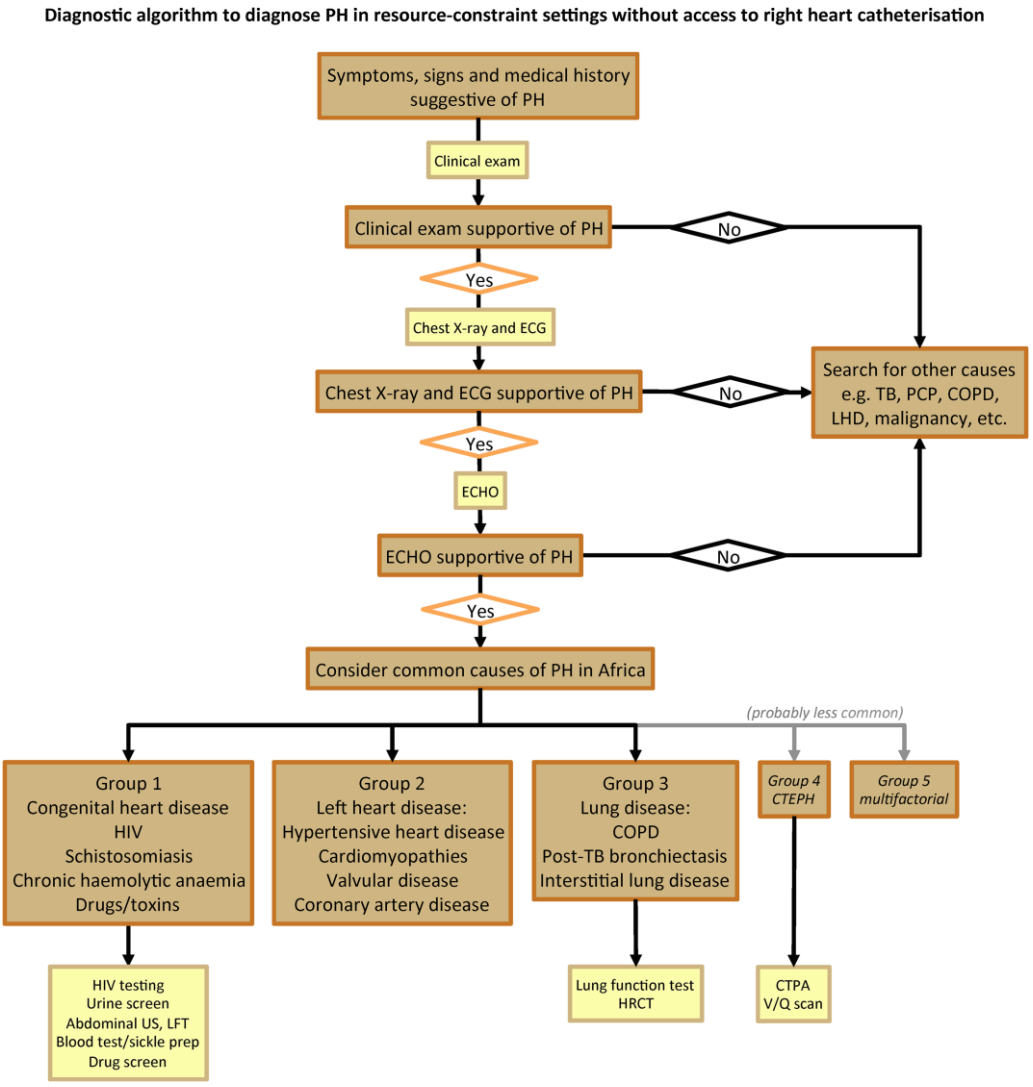

Figure 3 Diagnostic algorithm to diagnose pulmonary hypertension in resource-constraint settings. PH, pulmonary hypertension; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; ECHO, echocardiography; US, ultrasound; LFT, liver function tests; HRCT, high-resolution CT; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, CT pulmonary angiography; V/Q, ventilation/perfusion lung scan.

cost-effective. ECHO has become increasingly available in Africa and reliably allows the measurements to describe functional and morphological features of PH and to indirectly measure the pressures in the pulmonary artery; hence, to diagnose PH. Nonetheless, the exact measurements of the mean and systolic pulmonary artery are not possible, the PASP remains an estimate, and the use of ECHO to diagnose PH questionable.[35 36] A number of possible explanations for this 'inaccuracy' merit attention: (1) conditions for a reproducible calculation of PASP/RVSP include the presence of sufficient tricuspid regurgitation (TR) to produce a Doppler envelope and appropriate gain adjustments. An 'undergained' spectral signal will tend to result in underestimated PASP, whereas an 'overgained' spectral signal might overestimate the measurements; (2) careful adjustment of the transducer position and the use of colour flow Doppler are critical in order to reduce the Doppler angle and to obtain the maximal regurgitant flow velocity and severe TR will cause a laminar flow which invalidates the Bernoulli equation; (3) volume status and systemic blood pressure are other factors that potentially influence the measurement of PASP and (4) the highest value of RAP in the ASE guidelines is 15 mm Hg, but RAP measured by RHC can exceed 15 mm Hg. In spite of all these shortcomings, several studies have been published in the literature demonstrating the good sensitivity and specificity of ECHO versus RHC.[37–39] In the REVEAL registry, there was a good correlation in PASP between ECHO and RHC at baseline, even if repeated ECHO measurements alone were not sufficient to monitor changes in PASP or progression of PH.[40] In the first systematic review and meta-analysis addressing the diagnostic accuracy of ECHO in PH by Janda et al[41], the authors concluded that the correlation of PASP by ECHO compared with PASP by RHC was good with a summary correlation coefficient of 0.70 (95% CI 0.67 to 0.73). Also, the authors showed that the diagnostic accuracy of ECHO in PH was also

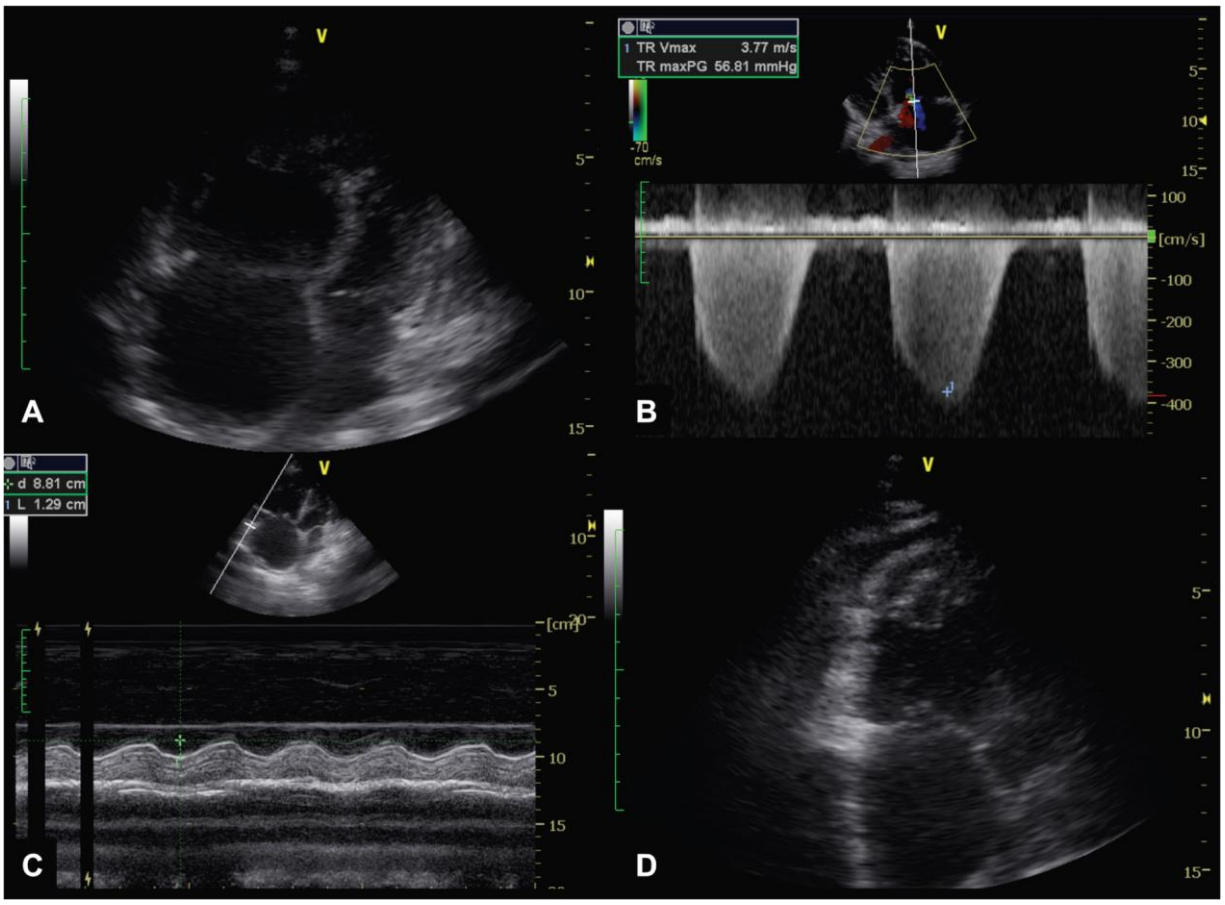

Figure 4 Diagnosing pulmonary hypertension using transthoracic two-dimensional Doppler echocardiography. (A) Four-chamber view showing grossly enlarged RV and RA; with right ventricularisation of the LV, and bulging of the RA into the LA; (B) Colour-wave and continuous-wave Doppler across the TV in the four-chamber view showing severe TR, despite the deceivingly less impressive colour-flow jet seen across the valve; (C) M-mode measurement of TAPSE depicting right ventricular systolic dysfunction; (D) Long-axis view of right ventricular apical thrombus. RA, right atrium; RV, right ventricle; LA, left atrium; TV, tricuspid valve; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane excursion.

acceptable with a summary sensitivity and specificity of 83% (95% CI 73% to 90%) and 72% (95% CI 53% to 85%), respectively. Additionally, Damy et al[42] demonstrated in their recent work that PASP when measured in 'good ECHO hands' is a strong predictor of mortality. Last but not the least, easily obtainable ECHO parameters like the E/A ratio, DCT and LA size can reliably distinguish between PH due to lung disease and PH due to left heart disease, allowing for the rapid triage of patients with a need for RHC. In summary, ECHO is far beyond a good modality to confirm both the presence and aetiology of PH in the majority of suspected cases when performed and interpreted by the requisite expertise under incorporation of all information obtained during a detailed ECHO assessment. ECHO will always provide incremental information in PH that cannot be obtained using RHC, whether in developed or developing countries.

Data cleaning process and statistical analysis

All study data will be collected on electronic case report forms and stored on a dedicated secure central database. Cases will be reviewed by at least two investigators (FT, AD, KS, AOM) for completeness and data validated. Query reports will be sent to the sites and resolved by the site investigators. If consensus on the WHO classification of PH cannot be reached, a third investigator's opinion will be requested. Data will then be verified and transferred to SPSS Statistics V.17.0 for all analyses by an independent team at Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Normally distributed continuous data will be presented as mean ±SD and non-Gaussian distributed variables as median +IQR. Categorical data will be presented as percentages with 95% CI where appropriate. For patient group comparisons, we will use χ^2 analysis with calculation of ORs and 95% CI (where appropriate) for discrete variables and Student t test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) will be performed on age, sex and baseline risk factors to derive adjusted ORs for the risk of presenting with PH/RHF overall, chronic lung disease and PH WHO Group 1. Significance will be accepted at the two-sided level of 0.05. ECG analysis will be subject to blinded coding according to the published Minnesota criteria to determine any pathological

abnormalities.[43] We aim to adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for this type of study wherever possible.[44]

PAPUCO substudies

Several substudies have been established within the PAPUCO registry. The ECHO substudy aims to describe in detail the ECHO characteristics of RV function in PH. The HIV-PAH substudy aims to describe the phenotype of HIV-PAH in Africa. The CHD and RHD substudies aim to describe the contribution of CHD and RHD to PH in Africa. In addition, serum will be collected at selected centres for studies on the biomarker profile. The HIV.INFLAME substudy aims to examine the role of inflammatory markers and oxidative stress on the development of HIV-PAH. We hypothesise that HIV-positive patients with PH have a proinflammatory state and raised markers of oxidative stress compared with healthy HIV-positive controls and that increased markers of inflammation and oxidative stress and decreased antioxidant capacity are predictors of outcome and indicators of disease severity.

Ethics and dissemination

All PAPUCO centres require ethical approval from their local ethics committee review board. Written informed consent must be obtained from every patient participating in the registry.

Study results will be disseminated in peer-reviewed journals. The first publication will include baseline and 6-month follow-up data from all centres. Substudy publications on the HIV cohort with a 24-month follow-up and the cohort of patients with PH due to left heart disease will be published after recruitment and follow-up has been completed. Laboratory-based research will be published after the work is completed.

The online data collection platform

A tailor-made database has been developed by integerafrica research and development to fulfil the study requirements. Open-source technology was used to develop the web-based system that allows investigators to collect, store, analyse, report on and export clinical research data. The interface is simple and user-friendly and leads the user through the data entry process. It anonymises personal patient data: data are stored as electronic case report forms on a secure, encrypted and backed-up server. It provides hierarchical permissions and validation at the point of data entry. Multimedia data formats, that is, scans of ECGs, CXRs and ECHO images, can be uploaded on the platform, allowing the storage of complete clinical records and data together. Tools for education, training and communication are installed within the web-portal. Frequently Asked Questions serve as a guide on how to use the platform. After secure login, documents such as paper case report forms, informed consent forms, study information sheets and patient education sheets on PH are available for download. All data can be exported in various formats for further analysis. The platform has been developed to cater for mobile internet connectivity available in most parts of Africa and a unique research platform far beyond a simple web-based database.

Recruitment process

Twelve centres have received ethics approval and are currently recruiting actively; an additional six countries are showing interest in joining the registry (figure 2). All

Table 1 Medical infrastructure at PAPUCO centres—diagnostic equipment and medical services

Centre	ECG	CXR	ECHO	RHC	CS	HRCT	CTPA	LFT	V/Q	Lab
CM01	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
CM02	X[1]	X[1]	X[1]	X[1]	X[1]					X[1]
CM03	X[1]	X[1]	X[1]							X[1]
MZ01	X	X	X							X
MZ02	X	X	X			X		X		X
NG01	X[1]	X[1]	X[1]			X[1]		X[1]		X[1]
NG02	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG03	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
NG04	X[1]	X[1]	X[1]							X[1]
NG05	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]		X[1]
SA01	X	X	X	X	X	X	X	X	X	X
SA02	X	X	X			X	X			X

CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; CS, cardiac surgery; CTPA, CT pulmonary angiography; CXR, chest X-ray; ECHO, echocardiography; HRCT, high-resolution CT; Lab, laboratory facility for haematology, chemistry, and microbiology; LFT, lung function tests; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG01, Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; NG04, Department of Medicine, University of Uyo Teaching Hospital, Uyo, Nigeria; NG05, Federal Medical Centre, Umuahia, Nigeria; RHC, right heart catheterisation; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg, South Africa and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa; V/Q, ventilation/perfusion lung scan; X, equipment/service available at the centre and free-of-charge for the patients; X[1], patients have to cover the costs for the service (out of pocket payments).

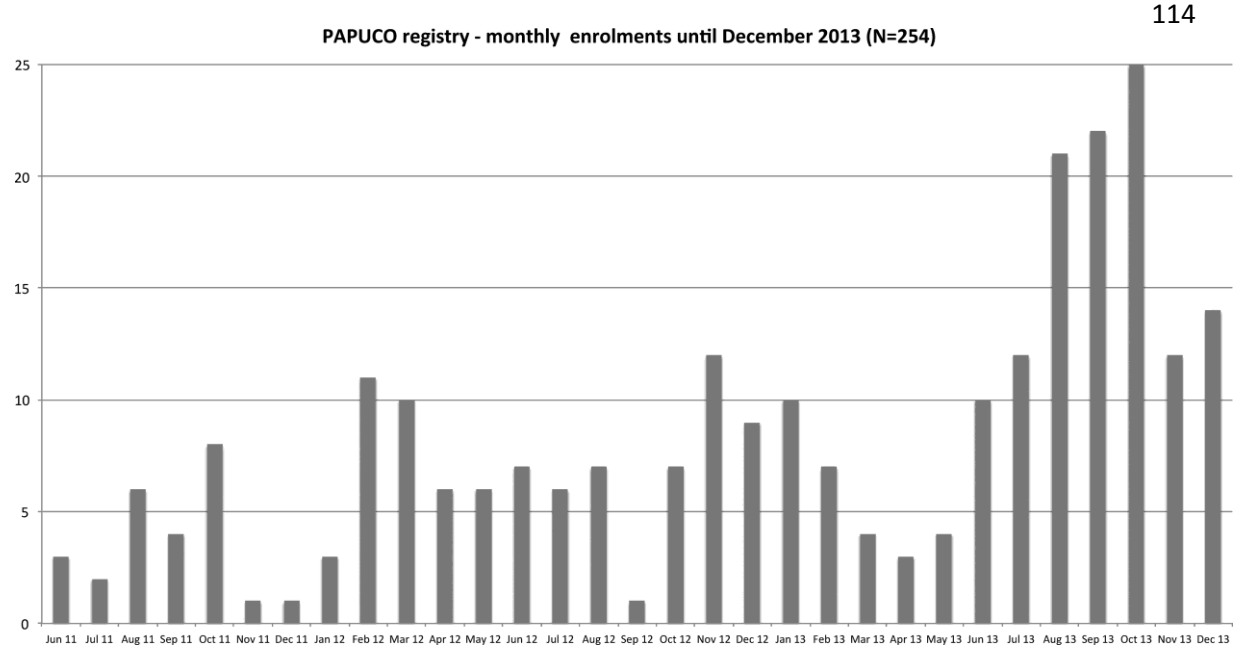

Figure 5 Pan African Pulmonary hypertension Cohort (PAPUCO) registry—monthly enrolment until December 2013. Number of patients recruited per month since the launch of the registry in May 2011.

centres are government-run public healthcare institutions with different medical infrastructure profiles, and all but one are cardiac centres within tertiary care hospitals (table 1); one centre is an infectious diseases referral clinic in South Africa. A total of 254 patients have been recruited until December 2013 (figure 5).

LIMITATIONS

The PAPUCO registry is an example of a functioning registry in low-resource settings. Limited resources should therefore not be seen as a limitation, but rather as a development opportunity. PAPUCO centres have different levels of medical infrastructure but not all patients will undergo the same rigorous workup in all centres, especially when compared with developed countries. Therefore, the clinical skills of the treating physician are often more important (and valuable!) than an additional diagnostic test in order to pin down the aetiology of PH in a patient. Moreover, patients often have to pay out of their pocket for diagnostic tests, and therefore accessibility to tests is limited due to the financial means of the patient. Although we aim for consecutive patient enrolment at each centre, we understand that this is often not feasible due to the high patient volume and workload of doctors.

SUMMARY

PAPUCO is a contemporary registry on PH in Africa using high international standards to diagnose PH. It will provide new insight on PH in Africa and ultimately improve diagnosis and care of patients. PAPUCO is already a showcase for registry activities in Africa and a vehicle to capacity generation and sustainable development in the healthcare sector. It interconnects health centres far beyond PH.

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Contributors KS, AOM and FT were responsible for the initial idea, literature review, and study design and planning. All authors have contributed not only to the set-up of the PAPUCO registry, but also to various aspects of the study design with input relating to their specific expertise in the field. FT, AD, AOM, LB, MUS, KMK, OSO, AM, PU, ASI, AD and KS have developed the study protocol. FT and KS wrote the study protocol. FT developed the database. FT, AD, AOM and KS cleaned the database. LB trained the doctors in echocardiography of the heart and developed the Echo protocol. AD trained doctors in Cameroon. OSO trained doctors in Nigeria. SS developed the statistical analysis plan. FT, AD, AOM, MUS, KMK, OSO, IM, AM, PU, KT, RB, AD and KS were substantially involved in data acquisition. All authors read and approved the final manuscript.

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REFERENCES

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34–41.
2. Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. Eur Heart J 2013;34:3538–46.
3. Sliwa K, Carrington MJ, Becker A, et al. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. Eur Heart J 2012;33:866–74.
4. Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008;371:915–22.
5. Stewart S, Mocumbi AO, Carrington MJ, et al. A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. Eur J Heart Fail 2011;13:1070–7.
6. Mocumbi AO, Lameira E, Yaksh A, et al. Challenges on the management of congenital heart disease in developing countries. Int J Cardiol 2011;148:285–8.
7. Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. Clin Res Cardiol 2010;99:65–74.
8. Sliwa K, Carrington M, Mayosi BM, et al. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. Eur Heart J 2010;31:719–27.
9. Stewart S, Wilkinson D, Hansen C, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. Circulation 2008;118:2360–7.
10. Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study. Cardiovasc J Afr 2007;18:295–9.
11. Karaye KM, Saidu H, Bala MS, et al. Prevalence, clinical characteristics and outcome of pulmonary hypertension among admitted heart failure patients. Ann Afr Med 2013;12:197–204.
12. Okello E, Wanzhu Z, Musoke C, et al. Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. Cardiovasc J Afr 2013;24:80–5.
13. Olusegun-Joseph DA, Ajuluchukwu JNA, Okany CC, et al. Echocardiographic patterns in treatment-naïve HIV-positive patients in Lagos, south-west Nigeria. Cardiovasc J Afr 2012;23:e1–6.
14. Chillo P, Bakari M, Lwakatare J. Echocardiographic diagnoses in HIV-infected patients presenting with cardiac symptoms at Muhimbili National Hospital in Dar es Salaam, Tanzania. Cardiovasc J Afr 2012;23:90–7.
15. Miller RF, Kaski JP, Hakim J, et al. Cardiac disease in adolescents with delayed diagnosis of vertically acquired HIV infection. Clin Infect Dis 2013;56:576–82.
16. Aliyu ZY, Gordeuk V, Sachdev V, et al. Prevalence and risk factors for pulmonary artery systolic hypertension among sickle cell disease patients in Nigeria. Am J Hematol 2008;83:485–90.
17. Mokhtar GM, Tantawy AAG, Adly AAM, et al. Clinicopathological and radiological study of Egyptian β-thalassemia intermedia and β-thalassemia major patients: relation to complications and response to therapy. Hemoglobin 2011;35:382–405.
18. Ahmed AEH, Ibrahim AS, Elshafie SM. Pulmonary hypertension in patients with treated pulmonary tuberculosis: analysis of 14 consecutive cases. Clin Med Insights Circ Respir Pulm Med 2011;5:1–5.
19. WHO. World Health Organization: The World Health Report 2013: research for universal health coverage. Euro Surveill 2013;18:20559.
20. Chu KM, Jayaraman S, Kyamanywa P, et al. Building research capacity in Africa: equity and global health collaborations. PLoS Med 2014;11:e1001612.
21. Noormahomed EV, Mocumbi AO, Preziosi M, et al. Strengthening research capacity through the medical education partnership initiative: the Mozambique experience. Hum Resour Health 2013;11:62.
22. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.
23. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54: S43–54.
24. WHO. WHO International Classification of Diseases (ICD). WHO, 1994.
25. Henry WL, DeMaria A, Gramiak R, et al. Report of the American Society of Echocardiography Committee on nomenclature and standards in two-dimensional echocardiography. Circulation 1980;62:212–17.
26. Jaffe CC, Weltin G. Echocardiography of the right side of the heart. Cardiol Clin 1992;10:41–57.
27. Sciomer S, Magrì D, Badagliacca R. Non-invasive assessment of pulmonary hypertension: Doppler-echocardiography. Pulm Pharmacol Ther 2007;20:135–40.
28. Beigel R, Cercek B, Luo H, et al. Noninvasive evaluation of right atrial pressure. J Am Soc Echocardiogr 2013;26:1033–42.
29. Quiñones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167–84.
30. Schachna L, Wigley FM, Chang B, et al. Age and risk of pulmonary arterial hypertension in scleroderma. Chest 2003;124:2098–104.
31. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 2006;174:1034–41.
32. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.
33. Barst RJ, Ertel SI, Beghetti M, et al. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011;37:665–77.
34. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol 2013;62:D117–26.
35. Penning S, Robinson KD, Major CA, et al. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. Am J Obstet Gynecol 2001;184:1568–70.
36. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615–21.
37. Lanzarini L, Fontana A, Campana C, et al. Two simple echo-Doppler measurements can accurately identify pulmonary hypertension in the large majority of patients with chronic heart failure. J Heart Lung Transplant 2005;24:745–54.
38. Laaban JP, Diebold B, Zelinski R, et al. Noninvasive estimation of systolic pulmonary artery pressure using Doppler echocardiography in patients with chronic obstructive pulmonary disease. Chest 1989;96:1258–62.
39. Matsuyama W, Ohkubo R, Michizono K, et al. Usefulness of transcutaneous Doppler jugular venous echo to predict pulmonary hypertension in COPD patients. Eur Respir J 2001;17:1128–31.
40. Farber HW, Foreman AJ, Miller DP, et al. REVEAL Registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension. Congest Heart Fail 2011;17:56–64.
41. Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. Heart 2011;97:612–22.
42. Damy T, Goode KM, Kallvikbacka-Bennett A, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. Eur Heart J 2010;31:2280–90.
43. Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic findings: standards and procedures for measurement and classification. Boston, Massachusetts: John Wright, 1982.
44. Elm von E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–8.

3.5. Handling of missing data

Missing data is a challenge in studies with longitudinal follow-up. In a review of cohort studies, it was found that the majority of studies included at least 10% of participants with some missing data and the amount of missing data ranged from 4 to 80% with a median of 25% (142). To overcome this both in the THESUS-HF and the PAPUCO registry, investigators systematically tracked all patients. Furthermore, in the PAPUCO study, a patient was considered loss to follow up only if he (or his next of kin) did not responded to telephone after more than 15 attempts on 3 different days. Also, data was rigorously cleaned and a query addressed to investigators in case of missing values. For variables that were insufficiently collected, there were theoretically two options to handle them. First, imputation of missing data; Second, excluding participants with missing data from analysis. In the THESUS-HF, multiple imputation was used while for the PAPUCO study we excluded participants with missing data in the analysis.

In the next four chapters we present the results of this PhD thesis in terms of condensed publications when the paper is under review in a peer-review journal or in terms of publications in peer-reviewed journals when already published.

Chapter 4. Baseline characteristics and outcome of patients with pulmonary hypertension in Africa: results of the Pan African Pulmonary hypertension Cohort study (PAPUCO).

4.1. Introduction

Chapter One of this thesis revealed that the epidemiology of pulmonary hypertension (PH) in Africa has yet to be fully characterized, although limited reports suggest that the incidence of PH in Africa is higher than that from high income countries, owing at least in part to the distinctively high prevalence of some risk factors of PH in the region (10, 110, 143) . Indeed, many known risk factors for PH are hyper endemic in Africa, including Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), rheumatic heart disease (RHD), hereditary hemoglobinopathies, schistosomiasis and other parasitic infections, and chronic hepatitis B and C infection. On one hand, a high prevalence of tuberculosis (TB), poorly treated asthma, high levels of pollution in urban areas and exposure to mining, may subsequently lead to various forms of pulmonary disease, PH and, often, to right heart failure (HF) with premature death. Furthermore, the high prevalence of RHD and endomyocardial fibrosis, the latter possibly also due to the high burden of parasitic infections, may contribute to secondary PH (144). On the other hand, Africa is in epidemiological transition with increased prevalence of non-communicable forms of heart disease such as hypertensive and ischemic heart disease. Left heart disease is the most common cause of heart failure in Africa and most likely a major contributor to PH and consecutive right HF (110, 118).

In this section we present data from the Pan African Pulmonary Hypertension Cohort (PAPUCO) study documenting the characteristics of PH in Africa, with a specific focus on the distribution of aetiologies of PH on the continent.

4.2. Methods

The methods relevant for this chapter has been described in details in Chapter 3. Below we focus on the statistical analysis for the data presented in the results section.

Statistical analysis

Data was transferred to SPSS Statistics 20.0 for all analyses. Continuous variables are presented as mean ± standard deviation or median (25^{th} - 75^{th} percentile), and categorical variables as percentages with the accompanying 95% confidence intervals (CI) where appropriate. Group comparisons used chi square ($\chi 2$) or Fisher exact test for categorical variables and Students t-test and analysis of the variance (ANOVA) or equivalent non-parametric tests (Kruskal-Wallis test) for continuous variables. To assess the predictors of mortality in the overall cohort, logistic regression was initially performed in a univariable analysis for each variable; then in an age and sex adjusted multivariable regression analyses with all variables in the model. Predictors entered into the model included distance walked in 6 minutes (alternatively as a continuous or categorical), TAPSE, RVSP and right HF. A p-value < 0.05 was used to characterize statistically significant results.

4.3. Results

4.3.1. Study cohort

At total of 254 patients with newly diagnosed pulmonary hypertension were included in the cohort study by 31^{st} December 2013 (Figure 21). Thirty four patients were excluded from data analysis due to either not meeting the inclusion criteria, or presence exclusion criteria or incomplete data. Eleven patients were below 18 years of age and were also excluded from analysis. Overall, 209 patients with newly diagnosed pulmonary hypertension were included in the analysis, of which 50% were recruited across three centers in Cameroon, Figure 21.

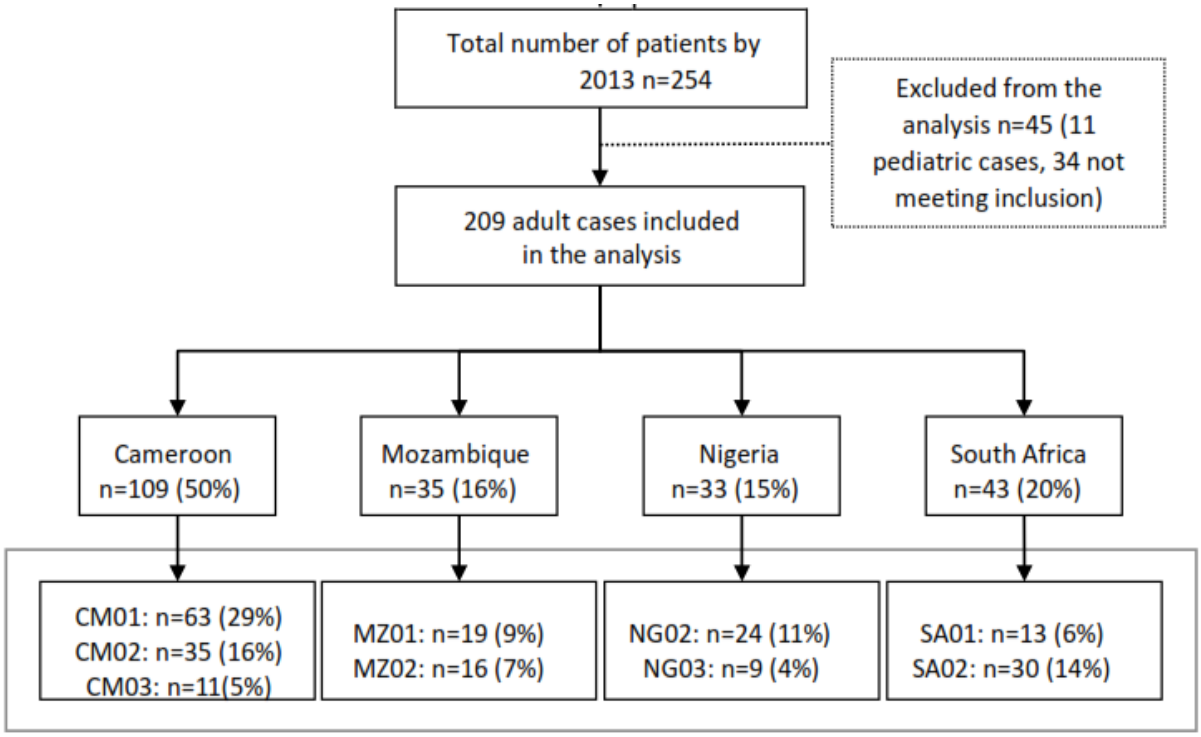

Figure 21: Flowchart showing the derivation of the overall cohort of 209 adult patients with pulmonary hypertension (PH) and the contribution of each center.

CM, Cameroon; MZ, Mozambique; NG, Nigeria; SA, South Africa.

4.3.2. Socio-demographic characteristics of the cohort members

The age of the cohort participants ranged from 19 to 98 years (mean age 48 years), 124 (59%) were women, and 203 (97%) African or of Black race (Table 15). 122 (58%) had completed only primary education or had no formal education and 63 (30%) lived in non-solid housing structures. Compared with men, women were more likely to live below the poverty threshold (42% vs. 25%, p=0.012). Table 15 shows the cardiovascular risk profile and co-morbidities of the cohort. Six patients had chronic liver disease, four Hepatitis B, one Hepatitis C, and one had schistosomiasis. 167 (80%) patients lived in areas endemic for schistosomiasis, 47 (22%) had a history of tuberculosis with 10 (5%) being on specific treatment at the time of their enrolment. HIV testing was performed in 134 (64%) patients of whom 47 (35%) were HIV-positive. Women were more likely to be exposed to indoor smoke from cooking or heating (without chimney) compared to men (p=0.0001), but men were more likely to be tobacco

smokers (<0.0001) and alcohol users (p=0.0004). Self-reported recreational drug abuse was rare (Table 15).

Table 15: Socio-demographic characteristics and risk factor profile of 209 adults (≥18 years) presenting with pulmonary hypertension

	All (n=209)	Men (n=85)	Women (n= 124)	P-value
Socio-demographic characteristics				
Median age, years (25th-75th percentiles)	48 (19-98)	54 (19-98)	43 (20-91)	0.094
African or black race	203 (97%)	83 (98%)	120 (97%)	>0.999
Education				
Completed only primary education	79 (38%)	35 (41%)	44 (35%)	0.468
Never went to school	46 (22%)	13 (15%)	33 (27%)	0.062
Income <30 USD per month	73 (35%)	21 (25%)	52 (42%)	0.012
Housing conditions				
Temporary shelter (e.g. shacks)	51 (24%)	18 (21%)	33 (27%)	0.414
Traditional hut	12 (6%)	2 (2%)	10 (8%)	0.128
Risk factor profile				
Cardiovascular risk factors				
Family history of CVD	69 (33%)	30 (25%)	39 (31%)	0.653
Hypercholesterolemia*	12 (6%)	8 (9%)	4 (3%)	0.072
Hypertension*	87 (42%)	42 (49%)	45 (36%)	0.064
Diabetes*	17 (8%)	9 (11%)	8 (6%)	0.310
Co-morbidities				
Haemolytic anaemia*	2 (1%)	2 (2%)	0	0.164
Rheumatic disease*	6 (3%)	1 (1%)	5 (4%)	0.404
Chronic liver disease*	6 (3%)	3 (4%)	3 (2%)	0.688
Chronic lung disease*	24 (11%)	11 (13%)	13 (10%)	0.660
Previous DVT/PE*	8 (4%)	4 (5%)	4 (3%)	0.717
Chronic infectious diseases				
Previous* or concurrent tuberculosis	47 (22%)	16 (19%)	31 (25%)	0.316
Concurrent tuberculosis	10 (5%)	3 (4%)	7 (6%)	0.741
HIV testing performed	133 (63.6%)	55 (64.7%)	78(62.9%)	0.6
HIV-infected	47 (22%)	14 (16%)	33 (27%)	0.09
Exposure to smoke and recreational drugs				
Indoor cooking/heating without chimney	66 (32%)	14 (16%)	52 (42%)	<0.001
History of smoking	26 (12%)	22 (26%)	4 (3%)	<0.001
Alcohol abuse	29 (14%)	21 (25%)	8 (6%)	<0.001
Recreational drug use	3 (1%)	3 (4%)	0	0.065

Data are presented as number (%) except for age presented as median (25th-75th percentiles). *diagnosed condition prior to presentation. Abbreviations: USD, US dollar; CVD, cardiovascular disease; DVT, deep vein thrombosis; PE, pulmonary embolism; HIV, human immunodeficiency syndrome.

4.3.3. Clinical characteristics

Table 16 summarizes important clinical findings. The most prevalent symptoms were shortness of breath (93%), fatigue (88%), palpitations (73%), and cough (60%). Women were more likely to experience dizziness compared to men (37% vs. 22%, p=0.0382). 66% of our cohort presented at WHO FC III or IV. The median Karnofsky performance Score was 70 (25^{th}-75^{th} percentiles: 50-80) and 71 (34%) patients could not walk further than 300 meters. Clinical parameters such as body mass index (BMI), heart rate, respiration rate, pulse oxymetry were similar in men and women. Systolic murmurs (n=119, 57%) and loud P2 (n=86, 41%) were the common pathological heart sounds.

Table 16: Clinical findings of 209 adults (≥18 years) presenting with pulmonary hypertension

	All (n=209)	Men (n=85)	Women (n= 124)	P-value
Symptoms at presentation				
Shortness of breath	194 (93%)	81 (95%)	113 (91%)	0.289
Cyanosis	26 (12%)	12 (14%)	14 (11%)	0.670
Cough	126 (60%)	57 (67%)	69 (56%)	0.114
Fatigue	184 (88%)	75 (88%)	109 (88%)	>0.999
Dizziness	65 (31%)	19 (22%)	46 (37%)	0.038
Syncope	15 (7%)	5 (6%)	10 (8%)	0.598
Palpitations	153 (73%)	62 (73%)	91 (73%)	>0.999
Chest pain	35 (17%)	15 (18%)	20 (16%)	0.851
WHO functional class (FC)				
WHO FC I/II	69 (33%)	20 (24%)	49 (40%)	0.017
WHO FC III	92 (44%)	46 (54%)	46 (37%)	0.016
WHO FC IV	46 (22%)	17 (20%)	29 (23%)	0.612
Karnofsky Performance Score	70 (50-80)	70 (60-80)	65 (50-80)	0.403
Distance walk in 6 minutes	252 (120-350)	275 (110-351)	234 (120-345)	0.803
6MWT <300 meters	71 (34%)	25 (29%)	51 (41%)	0.107
Body mass index, kg/m^2	23.4 (20.5-27.7)	23.5 (20.6-27.7)	23.3 (20.6-27.5)	0.615
Heart rate at rest (beats per min)	91 (76-100)	90 (72-98)	93 (80-102)	0.170
Systolic blood pressure (mmHg)	120 (108-133)	121 (110-137)	117 (107-130)	0.046
Diastolic blood pressure (mmHg)	77 (68-86)	78 (70-89)	76 (67-86)	0.130
Respiration rate at rest (breaths per min)	24 (20-29)	24 (20-28)	25 (20-30)	0.555
Pulse oxymetry at rest (%)	96 (92-98)	96 (91-98)	96 (92-98)	0.202
Cardiac auscultation				
Systolic murmur	119 (57%)	45 (53%)	74 (60%)	0.393
Loud P2	86 (41%)	31(36%)	55 (44%)	0.316

Data are presented as number (%) or median (25th-75th percentiles); *diagnosed condition prior to presentation. Abbreviations: WHO FC, World Health Organization functional class; 6MWT, 6-minutes' walk test.

4.3.4. Electrocardiographic, echocardiographic findings and signs of right heart failure at baseline

On electrocardiogram, 30 (14%) patients presented with atrial fibrillation, 48 (19%) with left ventricular hypertrophy and signs of right ventricular strain occurred in 30 (14%) and 39 (19%) for P-pulmonale and right ventricular hypertrophy respectively (Table 17). The median left ventricular ejection fraction was 46% (25^{th}-75^{th} percentiles: 35-65%), RVSP was 58 mmHg (25^{th}-75^{th} percentiles: 49-74 mmHg), and tricuspid annular plane systolic excursion (TAPSE) 13 mm (25^{th}-75^{th} percentiles: 11-17 mm). TAPSE was decreased (<15 mm) in 92 (44%) of patients. 78 (37%) presented in heart failure, defined as TAPSE <15mm and at least one clinical sign of heart failure (raised JVP or peripheral oedema). The median RVSP was 58 mmHg (25^{th}-75^{th} percentiles: 49-74 mmHg), and tricuspid annular plane systolic excursion (TAPSE) was 13 mm (25^{th}-75^{th} percentiles: 11-17 mm). Echocardiographic findings and signs of right are presented in Table 17 below, and were mostly similar in men and women.

Table 17: Electrocardiographic, echocardiographic findings and signs of right heart failure at baseline

	All (n=209)	Men (n=85)	Women (n= 124)	P-value
Electrocardiogram				
Sinus rhythm	92 (44%)	43 (51%)	49 (40%)	0.121
Sinus tachycardia	49 (23%)	15 (18%)	34 (27%)	0.134
Atrial fibrillation	30 (14%)	12 (14%)	18 (15%)	>0.999
P-pulmonale	30 (14%)	10 (12%)	20 (16%)	0.426
Right ventricular hypertrophy	39 (19%)	20 (24%)	19 (15%)	0.150
Left ventricular hypertrophy	48 (23%)	24 (28%)	24 (19%)	0.180
Chest X-ray				
Cardiomegaly	124 (59%)	41 (48%)	73 (59%)	0.157
Prominent pulmonary arteries	46 (22%)	14 (16%)	32 (26%)	0.853
Echocardiography				
Median LVEF (%)	46 (35-65)	45 (33-63)	48 (36-66)	0.299
Median RVSP (mmHg)	58 (49-74)	56 (50-70)	60 (48-74)	0.775
Median TAPSE (mm)	13 (11-17)	13 (10-17)	13 (11-16)	0.804
TAPSE <15 mm**	92 (44%)	35 (41%)	57 (46%)	0.570
Signs of right heart failure at baseline presentation				
Raised JVP	150 (72%)	63 (74%)	87 (70%)	0.639
Peripheral edema	134 (64%)	61 (72%)	73 (59%)	0.058
Raised JVP or peripheral edema	174 (83%)	75 (88%)	99 (80%)	0.132
Diagnosis of right heart failure*** at baseline presentation	78 (37%)	33 (39%)	45 (36%)	0.771

JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion. **TAPSE was assessed in 160/209 (77%) of patients. ***Right heart failure was diagnosed in patients meeting the following criteria: TAPSE <15 mm and at least one clinical sign of right heart failure (raised JVP or peripheral oedema).

4.3.5. Classification of pulmonary hypertension

Figure 22 below displays the distribution of our cohort by sex and by main groups of PH. In all, 34 (16%) were classified as Group 1: Pulmonary arterial hypertension. Table 18 provides details on the subgroup classification. HIV-associated PAH was the most common cause of PAH in Group 1 (n=17; 8%). 144 (69%) cases were classified Group 2: Pulmonary hypertension due to left heart disease (PH-LDH). Left ventricular systolic dysfunction was the most frequent cause of PH-LDH (n=80; 38%). 23 (11%) patients were diagnosed Group 3: Pulmonary hypertension due to lung disease and/or hypoxia. Tuberculosis-associated obstructive pulmonary disease (TOPD) was the most frequent cause of lung disease in our cohort. Four cases (2%) were classified Group 4: Chronic thromboembolic pulmonary hypertension and, again, 4 cases (2%) Group 5: Pulmonary hypertension with unclear multifactorial mechanisms.

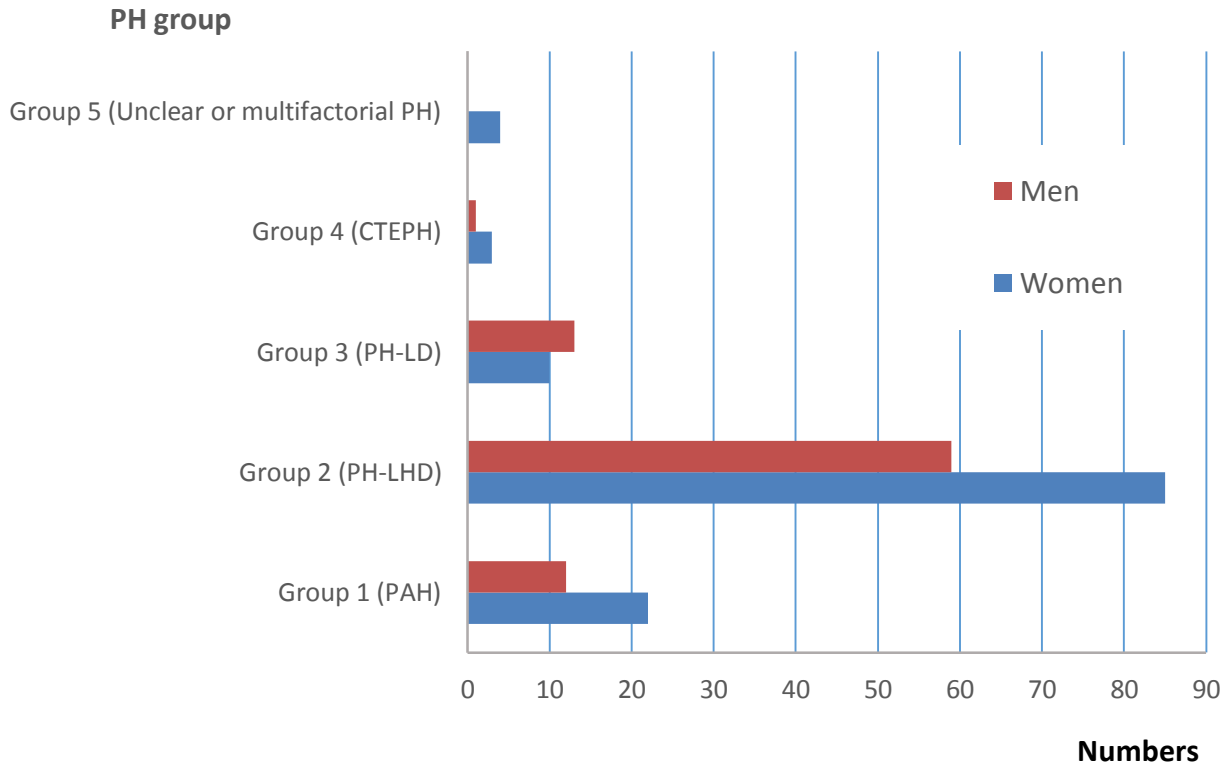

Figure 22: Distribution of main groups of pulmonary hypertension by sex

PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; PH-LD (LHD): PH due to lung disease (left heart disease); CTEPH: Chronic thromboembolic pulmonary hypertension.

Table 18: Subgroup classification of pulmonary hypertension

	Number	Percentage
Group 1: Pulmonary arterial hypertension (PAH)	**34**	**16%**
Idiopathic PAH	8	4%
HIV-associated PAH	17	8%
Congenital Heart Disease associated with PAH	8	4%
Schistosomiasis associated with PAH	1	0.5%
Group 2: Pulmonary hypertension due to left heart disease (PHLHD)	**144**	**69%**
Left ventricular systolic dysfunction	80	39%
Left ventricular diastolic dysfunction	35	24%
Valvular disease	29	14%
Group 3: Pulmonary hypertension due to lung disease and/or hypoxia	**23**	**11%**
Chronic obstructive pulmonary disease	7	3%
Tuberculosis-associated obstructive pulmonary disease	16	8%
Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)	**4**	**2%**
Group 5: Pulmonary hypertension with unclear multifactorial mechanisms	**4**	**2%**
Systemic disorders: vasculitis	2	1%
Other: endomyocardial fibrosis	2	1%

Data are presented as number (%). Abbreviation: HIV, Human Immunodeficiency Virus.

Table 19, we compare the clinical findings between the three major groups of PH. Patients in group 1 (PAH) were the youngest (median age 36 years) and those in group 2 (PH-LHD) were the oldest (median age 53 years). Female sex predominance was also noted in these two groups while patients in group 3 (PH due to lung disease) were more likely to be men and presented at a more advanced stage of the disease (87% in WHO functional class III/IV and median Karnofsky score = 70%). Group 1 exhibited the highest RVSP (median RVSP = 71 mm Hg) compared to group 2 and 3 (median RVSP = 58 and 59.5 mm Hg respectively). Lowest left ventricular ejection fraction was seen in group 2 (median EF = 40%), meanwhile, there was no difference in distance walked in 6 minutes nor in TAPSE between the three groups.

Table 19: Comparison of clinical findings between the three major groups of pulmonary hypertension

	Group 1 PAH (n=34)	**Group 2 PH-LHD (n=144)**	**Group 3 PH-LD (n=23)**	**P-value**
Age (years)	36 (20-69)	53 (19-98)	43 (21-91)	<0.001
Female (%)	22 (65%)	85 (59%)	10 (43%)	0.261
WHO FC III/IV	17 (50%)	107 (74%)	20 (87%)	0.004
Karnofsky Performance Score	80 (62.5-90)	70 (60.0-80.0)	70 (50.0-80.0)	0.033
Distance walk in 6 minutes	15.0 (120-401.3)	240 (120.0-345)	298.0(132-320)	0.777
Distance walk in 6 minutes <300 meters, n(%)	8 (23.5)	37 (25.6)	6 (26.1)	0.862
Echocardiography				
Median LVEF (%)	64(50-78)	40(29-59)	65(53.5-76.3)	<0.001
Median RVSP (mmHg)	71(56-95.0)	58(48.0-68.5)	59.5(49.8-67.8)	<0.001
Median TAPSE (mm)	14.5 (8.5-19.5)	13 (10-16)	12.5(11-18.5)	0.996
TAPSE <15 mm**	14 (50%)	65 (61.3%)	12 (60.0%)	0.601
Signs of heart failure at baseline presentation				
Raised JVP	21 (63.6%)	105 (75%)	18 (81.8%)	0.267
Peripheral edema	17 (50%)	97 (67.4%)	15 (65.2%)	0.699
Raised JVP or peripheral edema	27 (79.4%)	121 (84.0%)	20 (87.0%)	0.132
Diagnosis of right heart failure*** at baseline presentation	12 (44.5%)	54 (50.5%)	10 (50.0%)	0.485

Data are presented as number (%) or median (25^{th}-75^{th} percentiles) except for age (minimum-maximum); Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; LHD, left heard disease, LD, lung disease; WHO, World Health Organization; FC, functional class; 6MWT, 6-minutes' walk test; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion. ***Right heart failure was diagnosed in patients meeting the following criteria: TAPSE <15 mm and at least one clinical sign of right heart failure (raised JVP or peripheral oedema).

4.3.6. Clinical management

Prescription rates for Angiotensin Converting enzyme inhibitors/Angiotensin receptors blockers, beta blockers and digoxin showed a significant difference between the three groups and were especially higher in patients with PH-LLHD. Contrarily, prescription rates of calcium channel blockers targeting PH were higher in group 1 and 3, while there was no difference in prescription rates for anticoagulants and phosphodiesterase 5 inhibitors. Prescription rates of calcium channel blockers for systemic blood pressure lowering therapy also demonstrated a difference between groups with higher rate in PH-LHD. Medication use is presented in Figure 23.

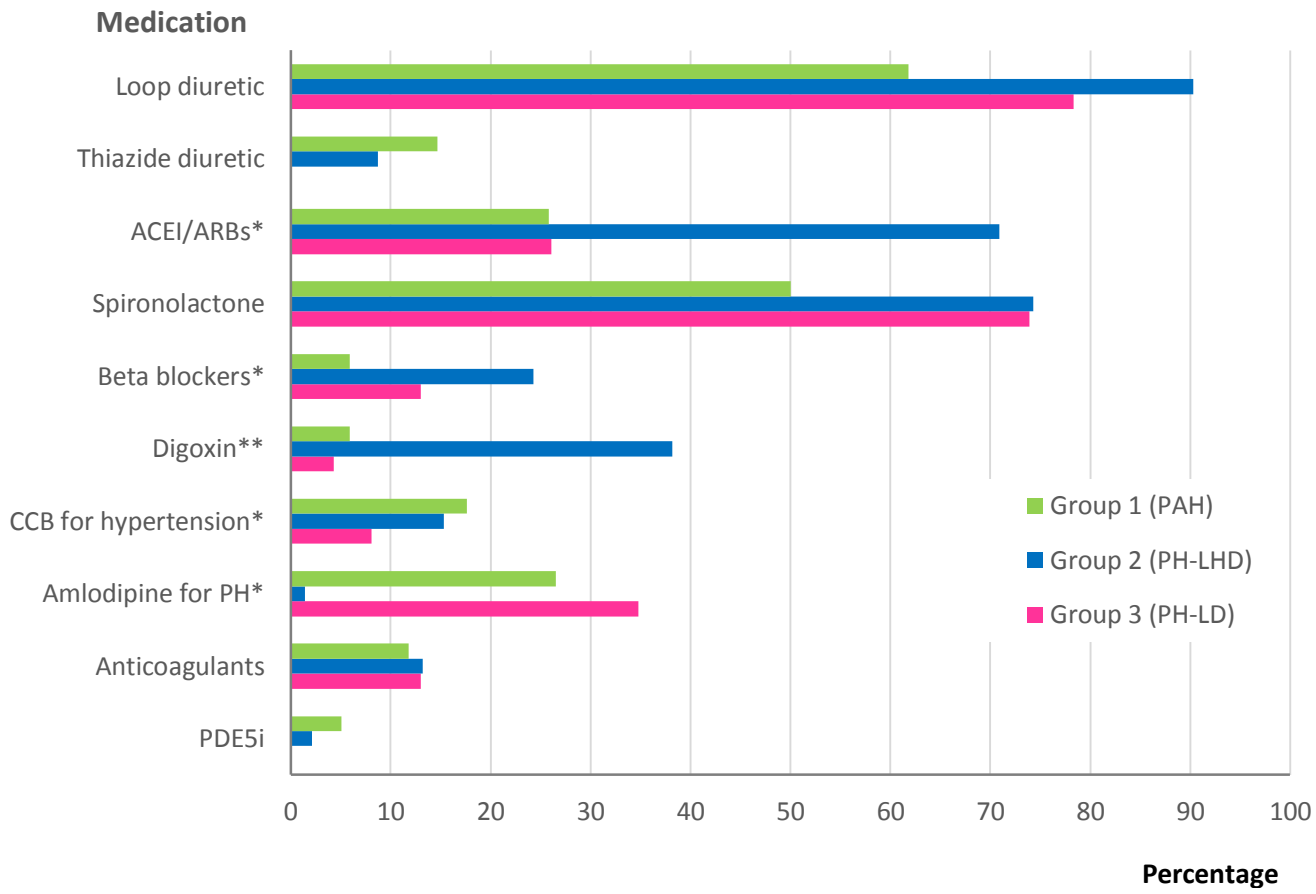

Figure 23: Pharmacotherapy according to pulmonary hypertension (PH) group in 209 sub-Saharan Africa patients with PH in the PAPUCO registry

ACEI: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptors blockers; CCB: Calcium channel blockers; PED5i: Phosphodiesterase 5 inhibitors; PH: pulmonary hypertension. * indicates p value < 0.05; ** indicates p-value < 0.001.

4.3.7. Follow-up and outcomes

Survival data at 6-month of follow-up was available for 91% of patients (189/209). In addition, 110 patients were followed up until data lock (31st December 2013). Median survival was 8.6 months (25th-75th percentiles: 6-15.2). 60/209 (29%) were reported dead. The Kaplan Meier curve for the overall cohort, for WHO functional class (I/II and II/IV), for PH groups 1, 2 and 3 and for hemodynamic grading mild, moderate and severe is shown in Figure 24. There was no significant difference in survival between groups.

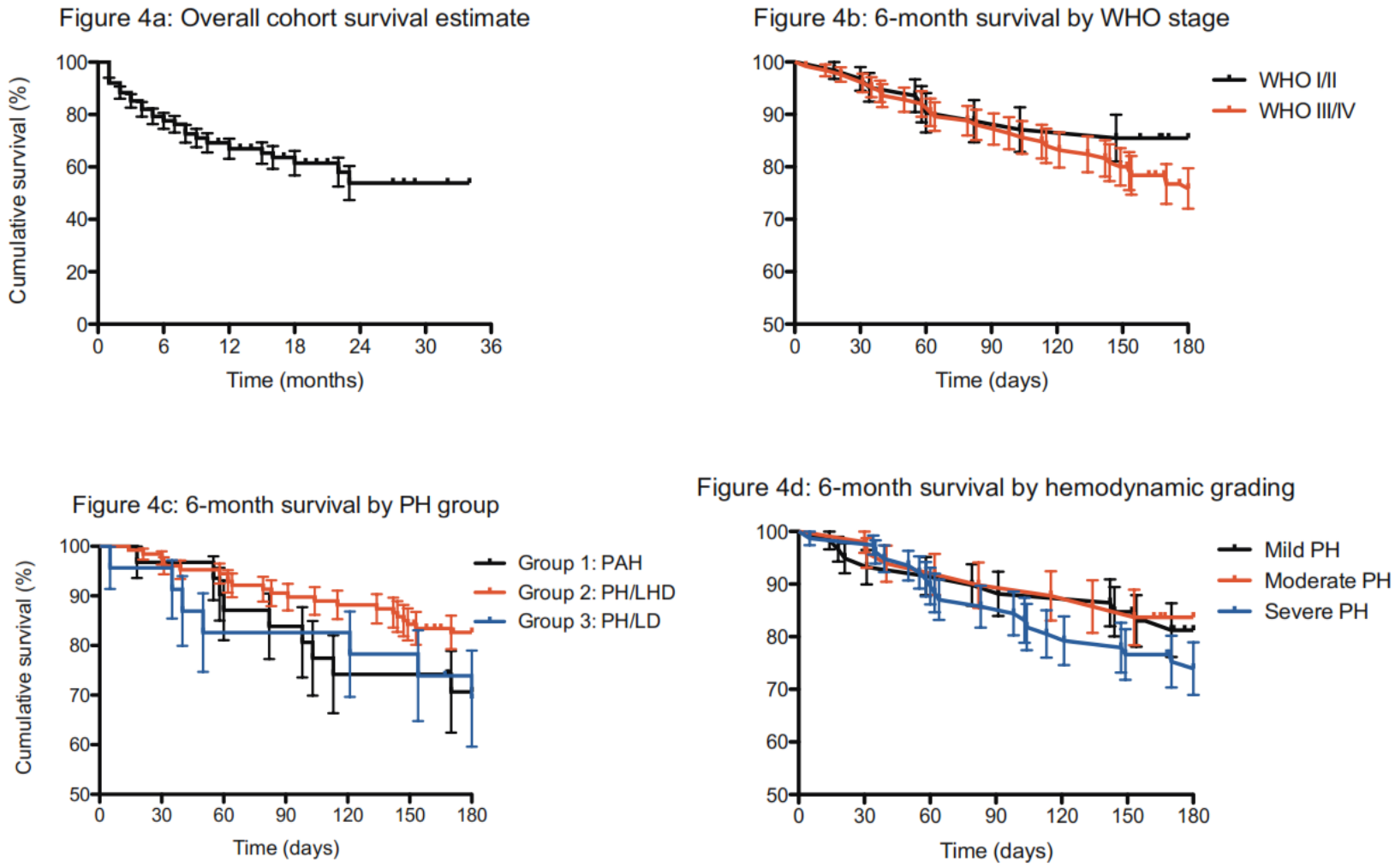

Figure 24: Kaplan Meier curves for survival by group in the PAPUCO registry.

Overall cohort (4a), by WHO functional class (4b), by PH groups 1, 2 and 3 (4c) and by PH hemodynamic grading (4d).

4.3.8. Predictors of mortality

In univariable analysis, none of the variables including age, sex, and distance walked in six minutes, RVSP, TAPSE were predictors of mortality. In an expanded multivariable analysis, with all the variables entered into the equation, only right heart failure [OR 3.501, CI (1.023 – 11.984), p= 0.046], but not RVSP [OR 1.022, CI (0.997 – 1.046)] and not TAPSE [OR 1.005, CI (0.926 – 1.091)] was an independent predictor of mortality (Table 20).

Table 20: Multivariable analysis predicting mortality in the overall pulmonary hypertension cohort from the PAPUCO registry

Variables	**Univariable analysis**	**Age and sex adjusted multivariable analysis**
	Odd ratio (95% CI)	**Odd ratio (95% CI)**
Age	1.008 (0.992 – 1.025)	0.698(0.229 – 2.129)
Sex	1.205 (0.641 – 2.265)	0.990(0.958-1.022)
Distance walk in 6 minutes	0.997 (0.994 – 1.000)	0.998 (0.994-1.002)
RVSP	1.012 (0.997 – 1.028)	1.022 (0.997 – 1.046)
TAPSE	0.960 (0.901 – 1.023)	1.005 (0.926 – 1.091)
Right heart failure**	0.537 (0.260 – 1.106)	3.501(1.023 – 11.984)

RVSP: right ventricular systolic pressure; TAPSE: tricuspid plan annular excursion; **Right heart failure was diagnosed in patients meeting the following criteria: TAPSE <15 mm and at least one clinical sign of right heart failure (raised JVP or peripheral oedema).

4.4. Discussion

The Pan African Pulmonary Hypertension Cohort (PAPUCO) represents the largest registry-type cohort study in patients diagnosed with PH ever conducted in Sub-Saharan Africa. It was designed to prospectively collect newly diagnosed cases of PH. Cases were collected between June 2011 and December 2013 and classified according to the updated Dana Point classification (53). At the data lock-point of the first phase of the registry 2013, 254 incident cases of PH were included and 220 patients analysed after a rigorous review process as pre-specified in the protocol to ensure highest data quality. An important difference between this registry and previous national or multinational registry designs is the broadening of the enrolment criteria to include patients of all groups of PH.

4.4.1. The distribution of PH aetiologies

The characterization of the multiple aetiologies of PH in Africa is leading to major advances in the understanding of this disease. We suspected that many known risk factors for PH that are hyper endemic in Africa including HIV/AIDS, rheumatic heart disease, hereditary haemoglobinopathies, schistosomiasis, other parasitic infections, and chronic hepatitis B and C infection were the primary cause of PH. This could be confirmed only partially. HIV/AIDS contributed to 17 cases (8%) accounted for a sizable proportion of PH in our cohort, although almost three times more patients were HIV-infected. Therefore, in Sub-Saharan Africa, the epicentre of the HIV epidemic, HIV should be considered more as co-morbidity than causative factor for PH, especially in the context when other risk factors of PH related to immunosuppression such as tuberculosis are present. In fact, most patients in Group 3 LH-LHD where found to have tuberculosis as the potential cause of PH, an expected finding for an endemic region for tuberculosis with disease notification rates reaching 1,500 per 100,000 population per year (145). In our study, PH-LHD was the most common type of PH, in line with existing reports, although studies on comparable prevalence amongst different groups of PH are lacking. Indeed, most existing registries had focus on a single group of PH (2, 146), except the European registry COMPERA (147), which is expected to be completed by May 2016 (148). The prevalence of PH-LHD in our study is similar to the 67.9% reported in the Armadale echocardiography cohort (61). In a large Italian echocardiographic cohort, Enea and

colleagues (149) reported that 52.6% had left heart disease, 7.5% lung disease, 1.3% chronic thromboembolic pulmonary hypertension, while 10.5% had unknown PH etiology. Differences in the prevalence of PH groups between studies are likely due to regional differences in the distribution of risk factors for PH, but also to variations in PH classification. That heart failure with reduced ejection fraction was the most common cause of PH-LHD in our cohort is consistent with the predominance of systolic heart failure in sub-Sahara Africa as reported in the THESUS-HF (118). Unlike previous reports in high income countries, our results showed that rheumatic valvular heart disease is still a frequent cause of PH in Sub-Sahara Africa, and this reflects not only the endemicity of the disease in this part of the world, but also late diagnosis. Indeed, in the Rheumatic Heart Disease Global Registry (REMEDY), Zühlke and colleagues (150) reported that up to 28% of cases present with PH-LHD.

4.4.2. The clinical profile of patients with PH

From a clinical standpoint, our findings revealed that PH is likely to affect poorly or uneducated women who are exposed to indoor fume. Moreover, patients presented late as illustrated by the high proportion of those with right heart failure, in severe WHO functional class (III/IV) and the short median distance on six minute walk tests. There is strong epidemiological evidence to support the female preponderance in Group 1 PH and the predominance of women particularly observed in "isolated" pulmonary arterial hypertension (PAH) (7, 69, 151). It remains unclear why PAH affects more women than men, but one of the most likely explanations is the predominance of connective tissue disorders in women, the role of sexual hormones as well as autoimmunity (152). Unlike PAH, one would expect sex distribution in other groups of PH to be largely influenced by the epidemiological features of the specific predisposing conditions. Yet, the female predominance was still evident in our cohort with dominance of left heart disease. The predominance of rheumatic heart disease in women (150) only partially accounts for this observation which merits further studies. The late detection of PH has been reported by several authors in PAH (69, 153). In the heart of Soweto study, Stewart et al reported that 28% of de novo cases of patients present with right heart failure (110). The reasons for this late presentation may include worldwide poor awareness of PH among physicians and the paucity of symptoms at the initial stage of the disease (2), but we cannot rule out some characteristics of health systems in SSA like a poor

referral system and socioeconomic issues. We believe efforts towards improving early diagnosis of the disease are warranted because at a late stage, response to therapy might not be optimal (154).

4.4.3. Medication and survival

Medication use in our cohort showed a high prescription rate for loop diuretics and spironolactone, a lower prescription rate for calcium antagonists and beta blockers, while very few patients were on disease modifying agents and anticoagulation. This medication use profile is largely influenced by the predominance of PH-LHD in our cohort. Diuretics are the basis of medical treatment for fluid control and relief of congestion, whereas angiotensin-converting enzyme inhibitors and β-blockers have proven efficacy in improving morbidity and long-term survival in patients with heart failure (54). The low uptake of anticoagulants is probably justified by difficulties in monitoring the treatment in SSA where limited access to high quality medical laboratories is common (155). Spironolactone was highly prescribed for its beneficial effect suggesting that endogenous aldosterone has an important role in the process of left ventricular remodeling in nonischemic patients with heart failure (156). However, in spite of this medication use, mortality rates were high in our cohort, highlighting the remaining diagnostic and treatment gaps. It is of note that except sildenafil and high dose calcium channel blockers which were essentially prescribed in group 1 and 3 PH of our cohort, other drugs approved for pulmonary arterial hypertension are not yet widely available across SSA. In addition, even if the hypothesis of targeting PH-LHD using these drugs has been very attractive, as described in Chapter 1 of this thesis, the results of randomized trials have been largely unsatisfactory. Regarding the high mortality rate in our cohort, only right heart failure was an independent predictor. In other registries of PH with larger sample and longer follow up, authors reported WHO functional class and PH severity to be significantly associated with poor outcome (69, 157). In the Armadale cohort (61), PH-LHD was associated with poor outcomes compared with other groups after a mean follow-up of 1060 days.

We recognize that our study had limitations. First as discussed in Chapter 2, right heart catheterization remains the gold standard for diagnosing PH but could not be used in this study due to its cost and unavailability in several centers. It shall be noted that, by including only patients with RVSP>35 mm Hg in a stable hemodynamic state we have increased our

chances of selecting true cases of PH. We did not systematically investigate all cases of PH using pulmonary function test which could have been justified to rule out COPD in women exposed to indoor fume. Our small sample size and short term follow up might have limited our capacity to carefully explore predictors of PH and outcome in this study. Last but not the least, the distribution of our data may not be entirely representative of all sub-Saharan Africa, as 50% of the patients were from Cameroon and, of nine cardiovascular centers contributing to this registry, only one was a rural centre. This limitation has to be understood in the context that very few health facilities in African countries have cardiac ultrasonography and cardiologists are rare. The contribution of the doctoral candidate has also driven this Cameroon dominance in the recruitment. Hopefully, these limitations will be addressed in the next phase of the registry, the PAPUCO 2 (123).

4.5. Conclusion

Findings from this first PAPUCO registry showed that all PH groups are present on the continent with PH-LHD being the dominant group, followed by group 1 and group 3. People affected are more likely to be young women who are poorly or uneducated and exposed to indoor fume, and they present at an advanced stage of the disease. A high short-term mortality was observed, principally driven by the occurrence of right heart failure, despite an acceptable use of medications for heart failure. We strongly believe a larger registry is warranted, more information on risk factors and specific PH groups profiles will lead to simple and affordable intervention studies. This is important to improve the quality of care and well-being of our patients and reduce the overall impact of disease in resource-constrained settings through more effective diagnostic and treatment strategies adapted to SSA.

Chapter 5. Pulmonary hypertension due to left heart disease: determinants of pulmonary pressures, clinical features, echocardiographic profiles and outcomes.

5.1. Introduction

In Chapter 1 of this thesis, we highlighted the importance of pulmonary hypertension due to left heart disease (PH-LHD) as the predominant type of pulmonary hypertension (PH), more frequently occurring as a manifestation of left heart systolic or diastolic dysfunction, but also to a lesser extend valvular disease. The existing reports have almost exclusively focused on selected groups of Caucasian patients with heart failure (HF), few using RHC, but the majority using non-invasive assessment of the right ventricular systolic pressure (RVSP) with echocardiography. Several studies of HF have reported that, compared with western countries, HF in sub Saharan Africa (SSA) populations occurs two decades earlier and is predominantly of non-ischemic origin, including some conditions that are now exceptional in western countries, but still has a poor prognosis (115, 118, 158, 159). How this particular phenotype of HF affects the landscape of PH-LHD and conversely how PH-LHD could influence HF prognosis in our region is still unknown, yet this information is needed to assist the stratification of patients with PH-LHD risk in daily clinical practice.

In this chapter, we investigated the determinants of pulmonary pressure, clinical and echocardiographic profile, outcome and their predictors in the specific population of patients with PH-LHD using the PAPUCO registry.

5.2. Methods

Study design, patients and clinical settings of the PAPUCO study were described in Chapter 2 of this thesis.

5.2.1. Definitions of terms

For all confirmed and enrolled patients with PH-LHD, additional data collection included the type of underlying left heart disease. HF with reduced ejection fraction (HFrEF) was defined as a clinical syndrome with 1) at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnoea, elevated jugular venous pressure, pulmonary crackles, a third heart sound, cardiomegaly on chest radiography, or pulmonary edema on chest radiography and 2) in the presence of a left ventricular ejection fraction (LVEF) <45%. HF with preserved EF (HFpEF) as presence of clinical HF with LVEF ≥45% and an echocardiographic evidence of elevated LV filling pressure evidenced by a dilated left atrium(160). Valvular heart disease (VHD) was diagnosed in patients with evidence of clinical and echocardiographic criteria (88). Participants were excluded from the PH-LHD sub-study if they had evidence for significant non-Group 2 causes of PH according to the WHO clinical classification.

5.2.2. Measurement of NT-pro Brain Natriuretic Peptide Levels

All subjects recruited in the study were invited to give their informed consent before extraction of blood for storage at the laboratory of the Hater Institute of Cardiovascular Research in Africa and subsequent testing for NT-PROBNP. In Chapter 2, we described the measurement technique of this biomarker.

5.2.3. Statistical analysis

Data were processed and analysed using the SPSS software version 20.0 for Windows. Based on previous studies, severe PH is usually defined by a RVSP >60 mmHg (161, 162). Patients with mild to moderate were arbitrarily categorized according to RVSP level as: mild if RVSP was 36-50 mmHg and moderate if RVSP was 51-60 mmHg. Categorical variables are presented as frequencies and percentages, while continuous variables are presented as means and

standard deviation (SD), or median (25^{th} to 75^{th}percentiles). Comparison between groups used appropriate parametric and non-parametric tests. Linear regressions were used to identify the independent predictors of RVSP. Kaplan Meier estimators was employed to depict the outcome (mortality or admissions) over time across major subgroups and differences assessed with the log rank test. Cox regressions were used to investigate the effect of PH on admissions within and between the three PH groups during follow up. Age, sex, EF, RVSP and TAPSE were first explored in a univariable and then in multivariable model after adjustment for age and sex (Table 26). A p-value <0.05 was considered statistically significant.

5.3. Results

5.3.1. General baseline characteristics of the study population

In Figure 25 below, we show the sequence for deriving the 202 patients with PH and the final PH-LHD cohort of 144 (71.3%) patients.

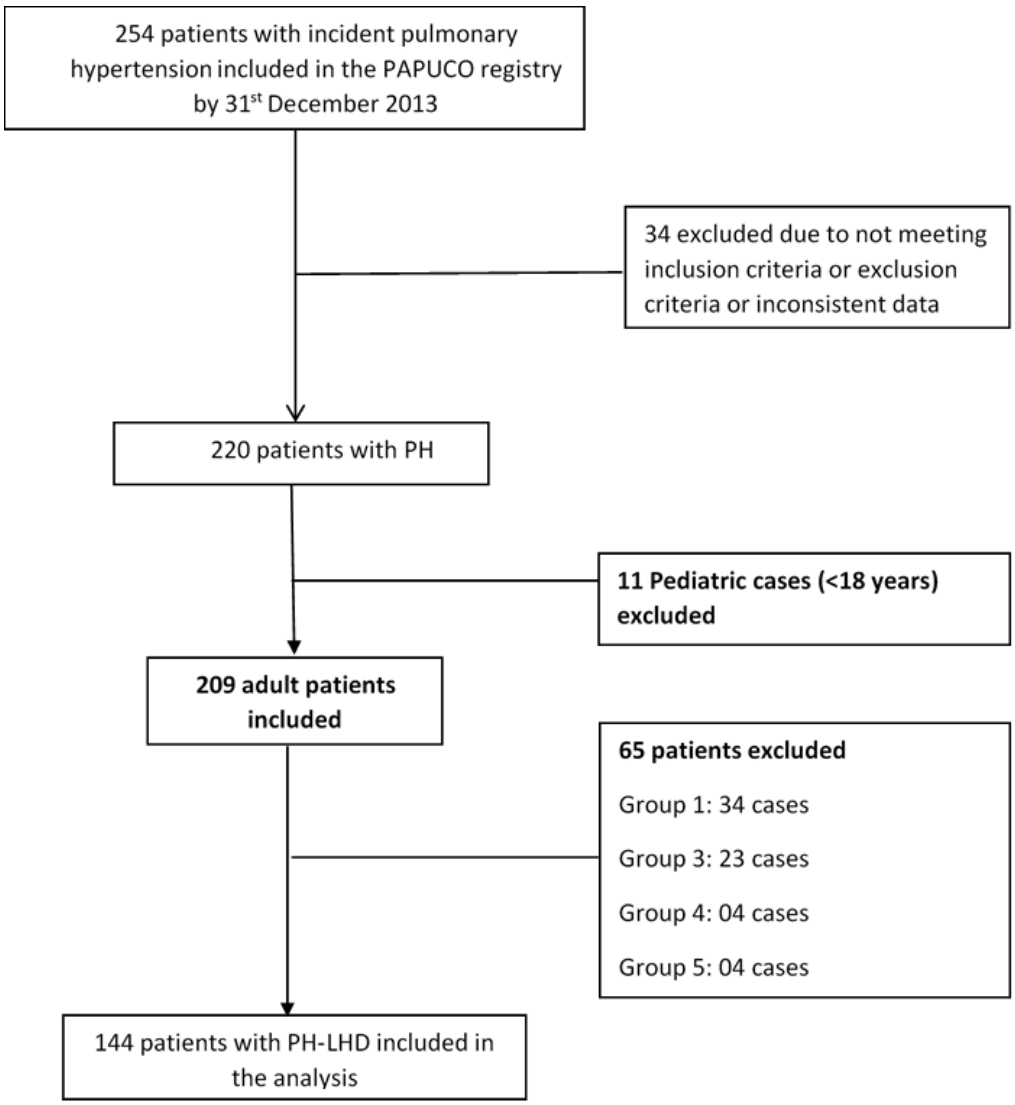

Figure 25: Flowchart showing the derivation of the pulmonary hypertension (PH) due to left heart disease cohort from the original PAPUCO all causes PH cohort.

5.3.2. PH, pulmonary hypertension; PH-LHD, PH due to left heart disease.

Table 21 depicts the socio-demographic and risk factor profiles of the PH-LHD cohort by sex. Women were more likely to be less educated and unemployed. Hypertension was found in 50.0% of patients, with predominance in men (59.3% vs. 43.5%, p=0.006). Women were more exposed to indoor cooking fumes (43.5% vs. 13.6%, p<0.001).

Table 21: Socio demographic and risk factor profiles of sub-Saharan African patients with pulmonary hypertension due to left heart disease in the PAPUCO registry

Characteristics	Overall	Men	Women	p-value
N (%)	144	59 (40.9)	85 (59.0)	
African or black race	140 (97.2)	57 (96.6)	83 (97.6)	0.543
Income below 30 USD	52 (36.1)	15 (25.4)	37 (43.5)	0.094
Never went to school	34 (23.6)	9 (15.3)	25 (29.4)	0.041
Unemployed	62 (43.1)	48 (56.5)	14 (23.7)	<0.001
Housing conditions				
Traditional housing or huts	9 (6.3)	3 (5.1)	7 (8.2)	0.192
Shack without sanitation	8 (5.5)	3 (5.1)	5 (8.6)	0.201
Cardiovascular risk factors				
Family history of CVD	49 (34.0)	21 (35.6)	28 (32.9)	0.220
Diabetes	16 (11.1)	8 (13.6)	8 (9.4)	0.347
Hypertension	72 (50.0)	35 (59.3)	37 (43.5)	0.006
Smoking	14 (9.9)	11 (18.6)	3 (3.5)	0.708
Hypercholesterolemia	12 (8.3)	8 (13.6)	4 (4.7)	0.102
Comorbidities				
COPD	4 (2.8)	2 (3.4)	2 (2.3)	0.842
Previous and/or concurrent tuberculosis	19 (11.8)	7 (8.5)	12 (14.1)	0.705
Concurrent tuberculosis	1 (0.7)	0	1 (1.2)	0.741
HIV-infected	16 (11.1)	7 (11.8)	9 (10.6)	0.711
Indoor cooking/heating	45 (31.2)	8 (13.6)	37 (43.5)	<0.001
Chronic liver disease	2 (1.4)	2 (3.4)	0	0.066
Alcohol abuse	19 (13.2)	15 (25.4)	4 (4.7)	0.014

Data are presented as number (%) or mean ± SD; Abbreviations: COPD, chronic obstructive pulmonary disease, CVD, cardiovascular disease; USD, US dollar; HIV, human immunodeficiency syndrome.

Table 22 depicts the baseline clinical features of the overall PH-LHD cohort by sex. The mean age (53.5±18.4 years) was similar between men and women. In all, 97 (67.4%) patients presented with

advanced stage disease, symptoms of WHO functional class III or IV, and reduced 6MWT distance (median 231.0 m and 33.3% less than 300 m). However, compared with women, men were more likely to present with late symptoms.

Table 22: Clinical findings of 144 sub Saharan African patients with pulmonary hypertension due to left heart disease in the PAPUCO registry

Clinical characteristics	All (n=144)	Men (n=59)	Women (n=85)	P value
Age (years)	53.5±18.4	56.4±15.5	51.1±20.0	0.093
Shortness of breath	138 (95.8)	59 (100)	79 (92.9)	0.034
Cyanosis	12 (8.3)	5 (8.5)	7 (8.2)	0.406
Fatigue	132 (91.7)	55 (93.2)	77 (90.6)	0.744
Dizziness	43 (29.9)	15 (25.4)	28 (32.9)	0.421
Palpitations	104 (72.2)	45 (76.3)	59 (69.4)	0.391
Shortness of breath	138 (95.8)	59 (100)	79 (92.9)	0.034
Cough	85 (59.0)	42 (71.2)	43 (50.6)	0.016
Peripheral edema	97 (67.4)	49 (83.1)	48 (56.5)	0.002
Raised jugular venous pressure	105 (72.9)	48 (81.4)	57 (67.1)	0.154
Heart rate (b.p.m)	89.4±19.7	87.9±21.1	90.4±18.7	0.458
Oxygen saturation (%)	95 (91 – 98)	97 (96 – 98)	95 (88 – 97)	0.546
Body mass index (kg/m²)	25.1±5.6	26.4±6.1	24.1±5.9	0.027
Systolic BP (mmHg)	125.8±28.7	131.3± 29.7	122.1± 27.8	0.063
Diastolic BP (mmHg)	79.2±18.2	79.2±16.5	81.1±18.7	0.373
WHO functional class III or IV	97 (67.8)	48 (82.8)	49 (57.6)	0.002
6 minute walk test distance (meters)	231.0 (100.0-335.0)	180.0 (112-316.7)	237.0 (127.-318.2)	0.471
6 minute walk test distance < 300 m	48 (33.3)	16 (27.1)	32 (37.6)	0.248
6 minute walk test not done	73 (50.7)	36 (61)	37 (43.5)	0.116

Data are presented as number (%), mean ± SD or median (25^{th} – 75^{th} percentile); statistical significance based on $p<0.05$. Abbreviations: BP, blood pressure; b.p.m, beat per minute; WHO, world health organization.

In Table 23, ECG and biological characteristics of our study population are presented with no significant difference between men and women.

Table 23: ECG and biological characteristics of our PH-LHD cohort

	All (n=144)	Men (n=59)	Women (n=85)	P value
Sinus rhythm	113 (78.4)	47 (79.7)	66 (77.6)	0.931
Sinus tachycardia	32 (22.2)	12 (20.3)	20 (23.5)	0.404
P-pulmonale	11 (8.6)	6 (11.3)	5 (6.7)	0.270
Right ventricular hypertrophy	16 (11.1)	9 (15.3)	7 (8.2)	0.187
Left ventricular hypertrophy	50 (34.7)	25 (42.4)	25 (29.4)	0.236
Atrial fibrillation/flutter	31 (21.5)	12 (20.3)	19 (22.4)	0.848
Haemoglobin (g/dL)	11.5±2.2	12.2±2.4	11.9±2.0	0.532
Serum creatinine (µmol/l)	96 (86.6 – 185)	97 (96 – 246)	89 (84.5 – 102)	0.410
CRP (mg/l)	29 (8.25 – 75.5)	12 (11.5 – 31)	46 (23 – 99)	0.627
NT-proBNP*	1196.8(424.4-2293.8)	1257.7(470.3-2376.1)	987.3 (416.0-1964.2)	0.440

Data are presented number (%) or mean ± SD; Abbreviations: CRP, C reactive protein.

ECG features and biological findings were similar between men and women. * Blood samples were available in 65 subjects with PH-LHD. 07 samples were haemolysed and not usable, hence NT-proBNP results were available in 58 subjects.

The medication used is presented in Figure 26 below. The prescription rates did not vary significantly in accordance with PH severity.

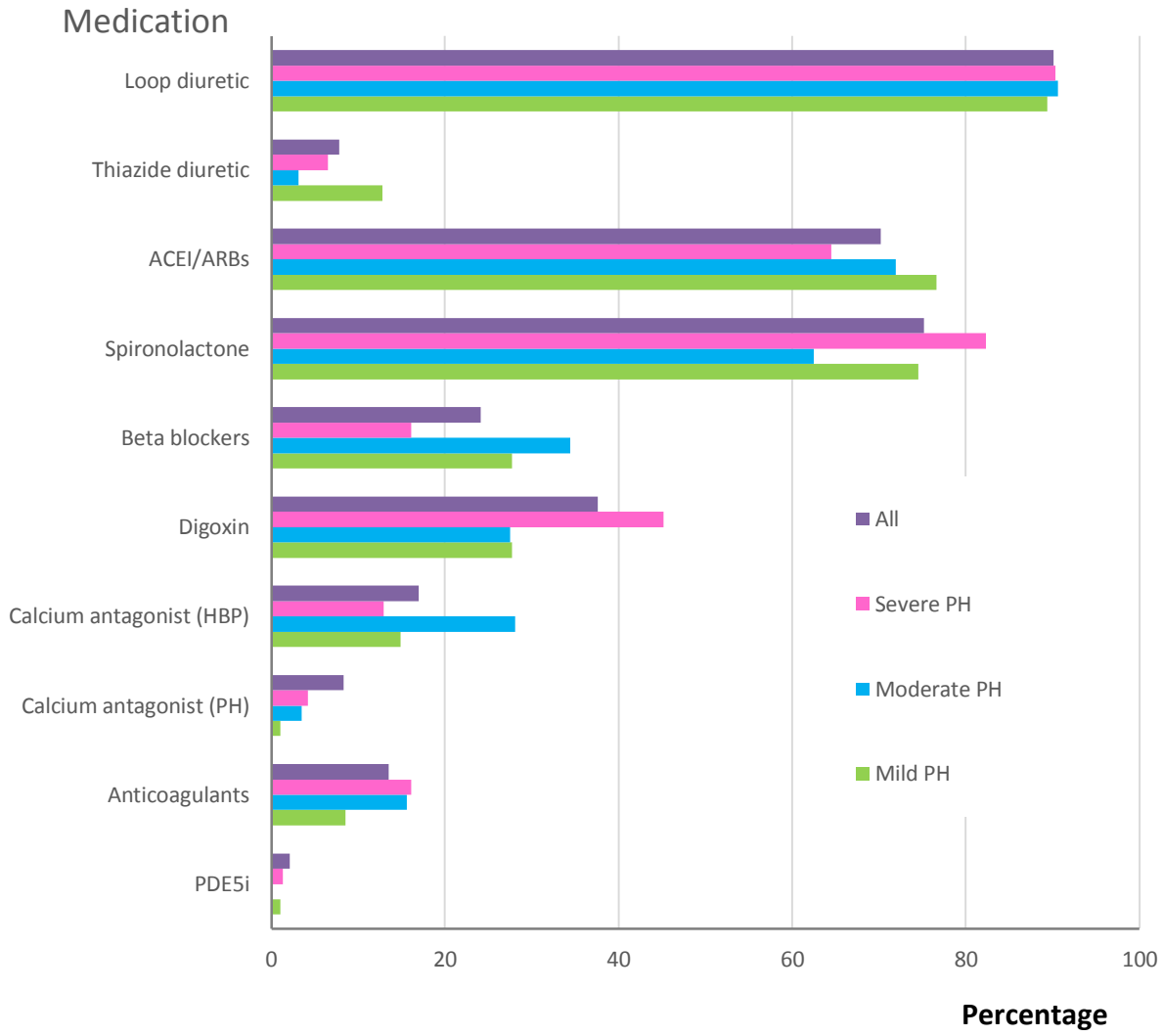

Figure 26: Pharmacotherapy according to pulmonary hypertension (PH) severity in 144 Sub-Saharan Africa patients with PH due to left heart disease in the PAPUCO registry.

Percentages represented are within PH categories. Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; HBP, high blood

Medications used did not vary significantly according to PH severity, and overall, less than 10% received a PH targeted therapy.

Baseline features and correlates of RVSP

As shown in Table 24 below, none of the clinical characteristics such as age, sex, hypertension and other risk factors, BMI, arrhythmia, heart rate, BP, haemoglobin, and serum creatinine correlated with RVSP in the PH-LHD cohort.

5.3.3. Baseline echocardiographic characteristics according to PH severity

Baseline echocardiographic variables according to PH severity are shown in Table 25. Mean baseline RVSP was 60.4±16.8 mm Hg, and values ranged from 36 to 107 mm Hg. Overall, patients with PH-LHD showed enlarged LA (LA diameter = 50.2±10.5 mm), dilated LV (LVEDD = 57.3±12.3), low EF (41.7±17.3 %), a high proportion of moderate-to-severe functional MR and TR (85.1 and 92.9% respectively), poor RV function (70.2 % with TAPSE < 15 mm and 66.7% with moderate-to-severely dilated RV).

There was no difference between the three groups with respect to LV dimensions, LV mass or EF, but EF tended to be higher in patients with severe PH (p= 0.06).

Table 24: Baseline characteristics across pulmonary hypertension (PH) associated with left heart disease categories in the PAPUCO registry

Characteristics	Mild PH	Moderate PH	Severe PH	P*	Overall	p**
	RVSP 36-50 mmHg (n=41)	51-60 mmHg (n=39)	RVSP>60 mmHg (n=64)		RVSP >35 mmHg	
Age, years)	52.2±17.1	53.6 ±17.4	53.9±20.4	0.660	53.5±18.4	0.081
Men, n (%)	15 (36.6)	23 (59.0)	21 (32.3)	0.506	59 (40.9)	0.395
Family history of CVD, n (%)	19 (13.5)	10 (7.1)	19 (13.5)	0.641	48 (34.0)	0.512
Diabetes, n (%)	8 (19.5)	3(7.7)	5 (7.8)	0.11	16 (11.1)	0.25
Hypertension, n (%)	21 (26.1)	22 (29.2)	29 (40.3)	0.219	72 (50.0)	0.318
Smoking, n (%)	8 (5.7)	5 (3.5)	1 (0.7)	0.703	14 (9.9)	0.708
BMI (kg/m^2)	25.6±4.7	24.5±4.4	25.7±7.1	0.690	25.2±5.7	0.703
Atrial fibrillation/flutter, n (%)	12 (8.3)	6 (4.2)	13 (9.1)	0.664	31 (21.5)	0.648
Haemoglobin (g/dL)	11.7±2.9	11.2±2.0	12.2±1.8	0.438	11.6±2.2	0.532
Serum creatinine (micromol/l)	151.3±69.2	132.4±91.1	125.5± 94.1	0.785	135.4±23.9	0.791
NT-PROBNP***	460.8 (109.9-321.8)	987.3(403.1-1901.6)	1235.4(438.9-20401.5)	0.112	1205.4 (424.4-	0.034
Heart rate (b.p.m.)	83.5±21.1	90.3±19.5	91.6±19.4	0.138	89.6±19.8	0.211
Systolic BP (mmHg)	128.6± 31.4	127.4± 26.5	123.8±29.6	0.451	125.4±28.7	0.467
Diastolic BP (mmHg)	81.1±18.7	79.2±16.5	78.3±16.5	0.326	79.2±18.2	0.373
6 min walk test distance (m)	222.4±138.8	211.3±139.6	235.1±139.6	0.549	221.1± 141.0	0.471

Data are presented as number (%) or me-an ± SD or median (25th – 75th percentiles); Abbreviations: BMI, body mass index; BP, blood pressure; b.p.m, beat per minute; COPD, Chronic obstructive pulmonary disease; CVD, cardiovascular disease; RVSP, right ventricular systolic pressure; 6MWT, 6-minutes' walk test. * (trend in the 3 groups); ** compared 1 vs. 3. *** NT-PROBNP results were available in 58 subjects.

Table 25: Echocardiographic characteristics across pulmonary hypertension associated with left heart disease (PH-LHD) categories and correlates of PH-LHD in the PAPUCO registry

Characteristics	Mild PH	Moderate PH	Severe PH	p-value*	Overall	p-value**	Correlation to RVSP	
	RVSP 36-50 mmHg	51-60 mmHg	RVSP >60 mmHg		RVSP >35 mmHg		R	P
Aortic root (mm)	29.8±4.1	29.7±5.4	30.1±5.7	0.997	29.9±5.3	0.991	0.48	0.587
Left atrium	47.5±8.0	49.2±9.2	53.8±12.5	0.024	50.2±10.5	0.016	0.227	0.008
IVSd (mm)	11.4±2.7	11.0±2.8	10.6±3.1	0.201	10.9±2.9	.0187	-	0.250
PWd (mm)	11.5±2.9	11.2±2.7	10.4±2.7	0.054	10.4±2.7	0.051	-	0.211
LVEDD (mm)	55.4±11.6	59.7±11.5	58.4±13.4	0.065	57.3±12.3	0.078	0.014	0.870
LVESD (mm)	43.7±13.4	48.3±13.9	44.3±16.0	0.478	44.8±14.5	0.527	-	0.321
LV mass indexed	123.2±61.	129.5±56.2	113.7± 36.9	0.072	117.4±38.2	0.081	-	0.353
LVEF (%)	41.4±	40.1±16.6	45.0±16.3	0.071	41.7±17.3	0.061	0.129	0.271
E wave (cm/s)[#]	97.8±28.2	70.5±53.1	99.9±55.2	0.297	85.2±51.9	0.312	0.093	0.431
A wave (cm/s)[#]	36.8±17.6	37.7±38.2	45.2±43.3	0.242	39.7±36.9	0.265	0.024	0.844
E/A ratio[#]	2.3± 1.3	2.6± 2.6	2.3± 2.2	0.806	2.2± 2.2	0.689	0.012	0.871
DT (ms)	115.6±34.	145.9±64.2	137.4±44.6	0.657	139.5±54.8	0.549	0.083	0.517
RVSP (mmHg)	41.6±3.1	53.1±4.4	78.1±12.7	0.000	60.4±16.8	0.000	-	-
TAPSE (mm)***	17.4±7.8	15.5±6.0	12.5±3.8	<0.0010	14.4±5.8	0.001	-	<0.001
TAPSE < 15 mm	9 (19.1)	12(37.5)	43(69.4)	<0.001	73 (70.2)	<0.001		-
RV size, mild, moderately to	15 (31.9)	16 (50.0)	35 (56.5)	0.012	94 (66.7)	0.036	0.283	0.005
Mild, moderate to severe MR	34 (24.1)	27 (19.1)	59 (41.8)	0.001	120 (85.1)	0.001	0.252	0.003

Data are presented as number (%) or mean ± SD; Abbreviations: DT, deceleration time; IVSd, interventricular septum in diastole; LVEF, left ventricular (LV) ejection fraction; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; MR, mitral regurgitation; PH, pulmonary hypertension; PWd, posterior wall in diastole; RV, right ventricular; RVSP, RV systolic pressure; TAPSE, Tricuspid annular plan systolic excursion; * (trend in the 3 groups); ** compared 1 vs. 3; ***TAPSE available in 101 subjects. [#] Doppler pattern of mitral inflow (E, A, E/A ratio) available in 99 subjects.

Figure 27 shows the prevalence of different aetiologies of PH-LHD by PH severity. Overall, HFrEF and HFpEF were observed in 55.6% and 24.3% respectively with no sex difference (29.9% and 13.2% in women vs. 26.4% and 10.4% in men, all p>0.05). VHD was predominant in women (overall 20.1%, 16.0% in women vs. 4.2% in men, p= 0.044). HFrEF was associated with a higher proportion (19.4%) of severe of PH-LHD. Mean RVSP according to LHD etiology was 57.6±15.5, 58.6±14.0 and 70.8±18.9 mmHg for HFrEF, HFpEF and VHD respectively (p<0.001 for linear trend).

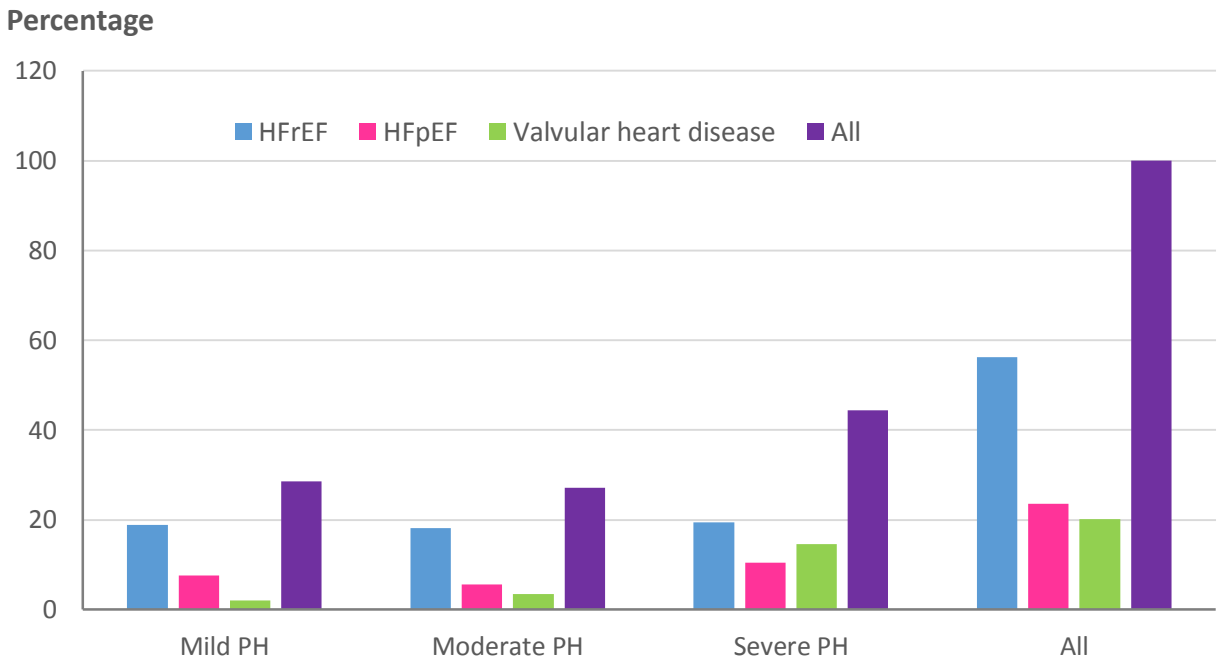

Figure 27: Classification of different type of left heart diseases in patients with pulmonary hypertension associated with left heat disease in the PAPUCO registry.

(Chi square, p=0.009). HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; VHD: Valvular heart disease; PH: pulmonary hypertension.

5.3.3.1. Echocardiographic correlates of pulmonary hypertension in the PAPUCO registry

RVSP correlated with LA diameter (r=0.227, p= 0.008, Figure 28 right panel) and TAPSE (r=-0.374, p<0.001, Figure 28 left panel). Of note, RVSP did not correlate with EF (p=0.271). In age and sex adjusted analysis, LA diameter (OR=0.58, 95% CI 0.31-0.85), grade of MR (OR=10.14, 95% CI 0.15-20.22) and TAPSE (OR=-0.98, 95% CI -1.55 to -0.46) were independent predictors of RVSP.

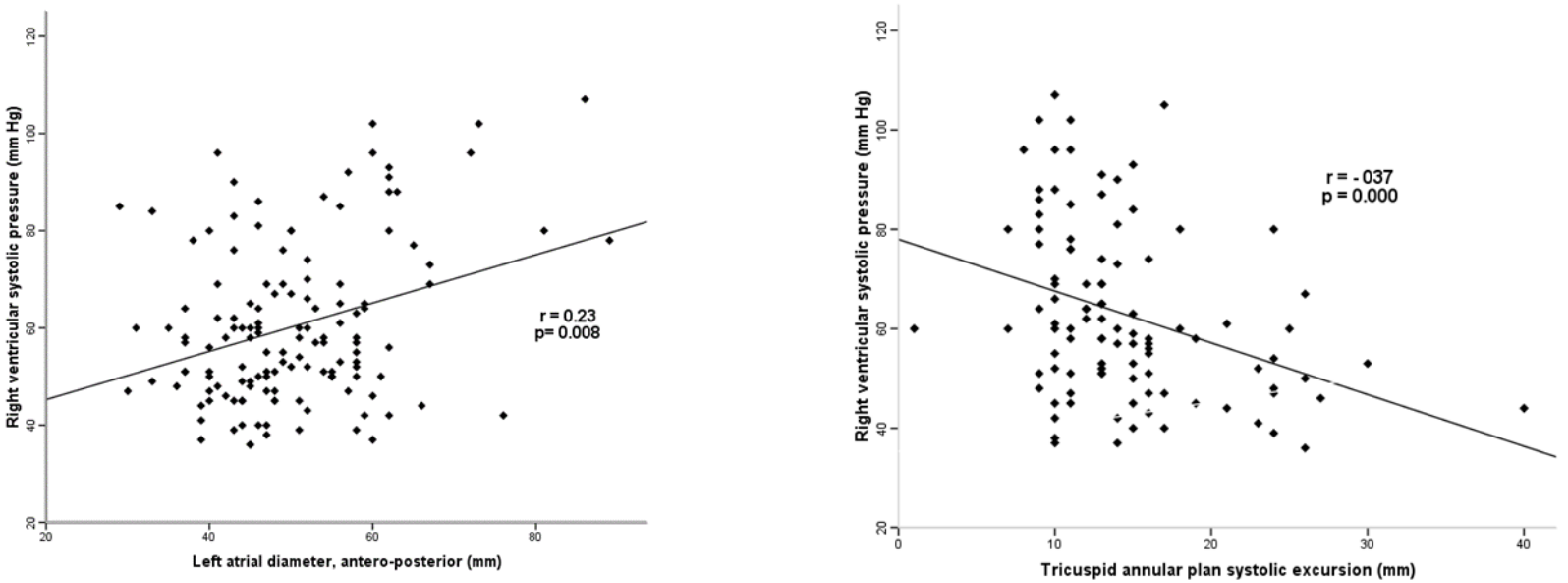

Figure 28: Correlations between right ventricular systolic pressure and left atrial size (left panel), and right ventricular function, as measured by the tricuspid annular plane systolic excursion (right panel).

5.3.4. Follow-up, mortality, admissions and predictor of admissions

The median follow-up period (25th-75th percentiles) for the overall cohort was 202 (58 - 231) days; during which 35 (cumulative incidence 24.6%) patients died and 43 (cumulative incidence 29.9%) were readmitted for heart failure. There was no significant difference in all-cause mortality between the three PH groups (χ^2 = 1.84, p = 0.392). However, as shown in Figure 29 below, there was a positive association between PH severity and admissions (log rank test, p=0.014).

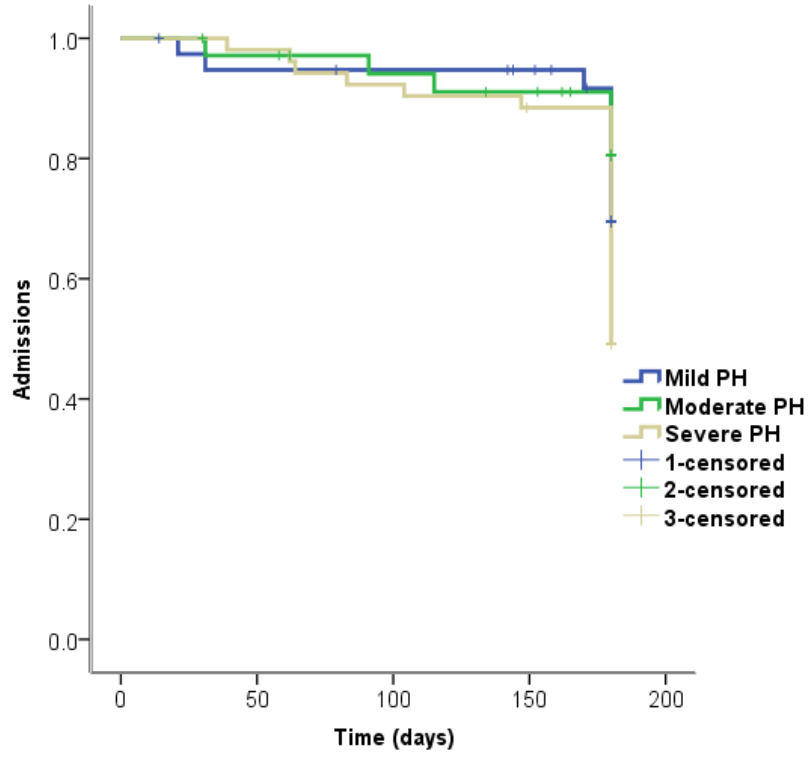

Figure 29: Kaplan Meier curves showing admissions by hemodynamic grading among patients with pulmonary hypertension associated with left heart disease in the PAPUCO registry.

(χ^2 from log rank test =8.47; p= 0.014).

In age adjusted Cox's regression models, age [HR: 1.01 (95% CI: 0.99 – 1.03), p= 0.425], ejection fraction [HR: 0.99 (0.98-1.02), p= 0.836] and TAPSE [HR: 1.05 (0.99-1.12), p= 0.094] were not significant predictors of admissions for HF; only RVSP [HR: 1.03 (1.01-1.07), p= 0.034] was an independent predictor of admissions for heart failure (Table 26).

Table 26: Multivariable analysis predicting admissions in the PH-LHD cohort from the PAPUCO registry

Variables	Univariable analysis	Multivariable analysis
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Age	1.02 (1.01 - 1.04)	0.98 (0.96 – 1.01)
Sex	0.79 (0.53 – 1.21)	0.63 (0.36 – 1.09)
EF	1.01 (0.99 – 1.03)	0.99 (0.98-1.02)
RVSP	1.03 (1.01 – 1.05)	1.03 (1.01 – 1.07)
TAPSE	1.02 (0.95 – 1.08)	1.05 (0.99 – 1.12)

EF: ejection fraction; RVSP: right ventricular systolic pressure; TAPSE: tricuspid plan annular excursion

5.4. Discussion

Data from this first prospective echocardiographic cohort-type registry of PH-LHD across four Sub-Saharan African countries revealed three major findings: First, PH-LHD is the main cause of PH and is commonly associated with LV dysfunction in Africa; Second, left atrial size and TAPSE are strong correlates of PH and; Third, patients present when they are symptomatic and PH is a predictor of admission risk within 6 months.

5.4.1. The clinical profile of patients with PH-LHD

In our study, PH-LHD affects relatively young people and our study indicates that it is especially predominant in unemployed women with low education. Hypertension was the most common cardiovascular risk factor with HFrEF the most frequent cause of PH-LHD and patients tend to present at advanced stages of disease. The latter is likely in part because they present when they are symptomatic, as it is not common for individuals to seek healthcare when they are well in many resource-constrained environments like those covered in this study. The young age of our population with PH-LHD is largely driven by early occurrence of LHD, especially HF in SSA. Female predominance has been inconsistently reported across PH-LHD studies. In the Heart of Soweto study, women were almost two-fold more likely to present with PAH (110). In one large community-based cohort study of PH-LHD in Minnesota, Bursi et al (62) reported equal sex representation, but more severe disease among women. Female preponderance in our study likely reflects poverty-related conditions such as indoor fumes from cooking, occurrence of rheumatic VHD with predominance in women and concurrent poor access to health care (163). A large number of hospital studies in high-income countries have shown male predominance of PH-LHD ranging from 54 to 68% (64, 67, 80, 161, 164). The dominance of HFrEF reflects the HF profile in low and middle income countries where the main contributors to the etiology of HF remain hypertensive heart disease, dilated cardiomyopathy and rheumatic valvular heart disease (VHD) which predominantly impact on systolic function (118, 165).

5.4.2. Determinants of pulmonary hypertension

Previous studies in patients with various left heart disease aetiologies have reported a close relation between elevated pulmonary artery pressures and elevated LV end diastolic pressures (67, 78, 89, 164) which both can lead to an increase in pulmonary vascular resistance and subsequent structural vascular remodelling, and right-sided failure. In our study, RVSP was independently correlated with LA size, severity of MR, and RV systolic function as assessed using TAPSE. It is likely that chronic elevation of LV filling pressures due to LV dysfunction in these patients translated into left atrial enlargement, which then led to an increase in RVSP. Our findings are similar to previous studies in which specific cardiac structural abnormalities correlated with PH-LHD (67, 164). These findings suggest that despite their relative young age, our patients presented at advanced disease when severe PH had already caused RV dysfunction; this can therefore explain the more severe symptoms and reduced exercise capacity. Similarly, Stewart et al (110) reported that up to 28% of *de novo* cases of heart failure in the Heart of Soweto study presented with right heart failure. Except NT-PROBNP, none of the clinical or biological characteristics were associated with increased RVSP, similar to findings in research conducted by Damy et al (67). Nevertheless, because it has been well established that RVSP increases with age (85, 166), we cannot rule that the absence of correlation between age and RVSP in our study could simply be due to the younger age our population. That NT-proBNP was higher in patients with severe compared with mild PH-LHD may suggest a relationship worth exploring between RV structure and function (167) in PH. This requires confirmation on a larger sample.

5.4.3. Short term mortality and hospital admission in PH-LHD

In the systematic review presented in the background Chapter (119), we found PH to be almost invariably associated with increased mortality, but information on readmission for heart failure was limited. Short term admissions were frequent in our sample, and correlated with PH severity. Considering the younger age of our population and relatively better systolic function, our admission rate looks high, and could be due to late presentation or health system factors. Indeed, using similar diagnostic criteria, Mutlak et al (168) reported a lower 12-month rehospitalisation rate (9.2%) in patients with PH due to HF following acute

myocardial infarction. In the ESCAPE trial of patients with severe HFrEF, the 6-month re-hospitalization rate was 50% in patients with PH, but PH failed to predict admissions (81). Other studies of PH-LHD with longer follow-up (63, 75, 76, 168, 169) have reported similar results.

PH has been almost invariably shown to inversely affect mortality in patients with left heart disease (119) and RV dysfunction is a marker of poor prognosis in HF (133). Some possible explanations of the absence of lack of effects in our cohort include: 1) the small sample size, especially given the heterogeneity of the affected population; 2) with up to 70.2% of patients having a poor RV function, the discriminatory power markers of RV function for mortality risk will drop. It remains possible however that a difference could be observed in a longer follow up of a larger sample.

5.4.4. Strengths and limitations

Most limitations discussed in chapter 2 and 3 of this thesis apply. This includes our diagnostic methods for PH (echocardiogram without confirmation by RHC), the small sample size and the short term follow up. It is of note that Doppler echocardiography is the most commonly employed diagnostic tool in clinical practice for diagnosis and follow up of the majority of LHD. Second, as discussed in Chapter 3, the classification of PH in limited resource settings with high prevalence of major risk factors remains an enormous global health challenge. We cannot rule out that some women exposed to indoor smoke might have a lesser degree of obstructive pulmonary disease which could overlap with left heart disease and aggravate PH. Third, we did not record enough detailed measures of diastolic function; Doppler tissue imaging indices would have contributed in better characterization of HFpEF(78). Finally, the small number of patients who consented for blood sample extraction limited investigation of the role of NT-PROBNP in diagnosis and prognosis of PH.

5.5. Conclusion

In this study, we have shown that a simple and quick estimation of RVSP by echocardiography in low-resource settings is feasible within a prospective cohort design, and can give reliable

information both on baseline status and future outcomes. Pulmonary hypertension due to left heart disease affected people of relatively young age; LA size, TAPSE and severity of MR were strong correlates, and PH was an independent predictor of subsequent HF admissions. This indicates that an increase in RVSP in our setting identifies a group of patients prone to develop clinical congestive heart failure. A long term follow-up of a larger sample is necessary to confirm these observations.

Chapter 6. Prevalence and predictive utility of specific ECG criteria of right ventricular hypertrophy and right atrial enlargement in pulmonary hypertension: Evidence from the Pan African Pulmonary hypertension Cohort (PAPUCO) study.

6.1. Introduction

Despite the improvements in understanding PH and developing novel therapies, the condition is still diagnosed at the advanced stage in a significant proportion of patients, due to the paucity of symptoms in early stage of the disease. This has negative impacts on subsequent quality of life and survival (141). The American College of Cardiology/American Heart Association (31) and the European Society of Cardiology/European Respiratory Society (141) guidelines recommend ECG as an initial tool in exploring patients with suspected PH based on studies conducted predominantly in patients with PAH. However, these guidelines consider ECG to be an inadequate tool for screening, and emphasize on the advantage of Doppler echocardiography.

In SSA where chronic and endemic precursors of PH including chronic infectious diseases, hypertensive heart disease, cardiomyopathy and rheumatic heart disease are highly prevalent, early diagnosis of PH is of particular importance. The high cost, low availability, and the need of expertise for echocardiography limits its utility in this part of the world and justifies the interest in alternative tests like ECG. ECG abnormalities in patients with PH have been predominantly described from western registries of PH (170-174). In this chapter, we

aimed to assess the predictive value of an affordable, widely available, objective and reproducible test like ECG to diagnose PH in resources-limited settings.

6.2. Methods

6.2.1. Study design, patients and clinical settings

The purpose and methods of the PAPUCO study has been described in Chapter 2.

6.2.2. Electrocardiogram selections and interpretation in patients and control subjects

We searched ECGs from the PAPUCO registry to identify all patients who had both Doppler Echocardiography and 12-lead ECG performed within a forty eight hour interval of their baseline inclusion. We excluded all patients with pacemakers (due to inapplicability of standard ECG criteria), poor quality ECG and those without measurable RVSP. Control subjects were patients with normal Doppler echocardiography and RVSP less than 35 mm Hg who underwent ECG recording during their baseline inclusion in the Heart of Soweto Study (28). All ECGs were reviewed and interpreted by two independent board certified cardiologists who were blinded to clinical and echocardiography results. Disagreements were resolved by consensus and if could not be reached, a third opinion was requested. We electively studied pre-specified ECG patterns classified into minor or major abnormalities (Table 27) as previously described in a large African cohort of heart disease-free Africans (175). The following ECG patterns suggestive of right heart strain (Table 27) were particularly studied: 1) QRS axis ≥ 100°; 2) R/S ratio >1 or RV1 >7 mm; 3) right ventricular hypertrophy (RVH) defined as a QRS axis ≥ +100°; and R/S ratio ≥1 or R in V1 >7mm, right bundle branch block associated with QRS right axis deviation (≥ 100°), and P-pulmonale.

6.2.3. Statistical analysis

All statistical analyses were performed with SPSS 20.0, Chicago, Illinois. Prevalence, sensitivity (Se), specificity (Sp), and positive (or negative) predictive values (PPV or NPV) of ECG patterns suggestive of right heart strain were calculated by the following formulas (19, 90):

- Prevalence of an ECG abnormality = Total with the abnormality of interest/total number of patients in the group of interest.
- Se = True positive/(True positive +False negative) x 100
- Sp = True negative/ (True negative + False positive) x 100
- PPV = $[Sensitivity\ x\ prevalence] \div [Sensitivity\ x\ prevalence + (1 - specificity) * (1 - prevalence)]$
- NPV = $[Specificity\ x\ (1 - prevalence)] \div [Specificity\ x\ (1 - prevalence) + (1 - sensitivity) * prevalence]$

Prevalence, Se, Sp, PPV, NPV are presented as percentages, while continuous variables are presented as means and standard deviation (SD), or median (25th to 75th percentiles). We used χ^2 to compare proportions of categorical variables and student t test to compare mean for continuous variables. A p-value <0.05 was considered statistically significant.

Table 27: Classification of electrocardiographic abnormalities (176)

Minor abnormalities	**Major abnormalities**
Sinus tachycardia (>100 bpm) Minor T-wave changes (T-wave flattening) or early repolarization Definitive right ventricular hypertrophy • QRS axis ≥ +100° • R/S ratio ≥1, or R V1 >7mm RBBB + QRS axis ≥ +100°	Major T-wave abnormalities (T-wave inversion) Left ventricular hypertrophy Cornell voltage criteria for LVH • S in V3 + R in aVL >24mm (men) • S in V3 + R in aVL >20mm (women) Pathological Q waves Prolonged QTc (>470ms as calculated by Bazett's formula) LBBB or other conduction delay P-pulmonale: P wave in lead II > 2 mm, or >1.5mm in lead V_1/V_2, unchanged duration
RBBB: right bundle branch block, LVH: left ventricular hypertrophy, LBBB: left bundle branch block	

6.3. Results

6.3.1. Clinical characteristics

Table 28 depicts the clinical characteristics of the 65 patients with PH. Patients were young (mean age = 47±14 years), 21 (32%) were men, and all except four were of Black African origin. The control subjects were younger with a mean age of 36 ±10 years and 48 (16%) were males. All demographic, clinical and echocardiographic profile were similar between men and women in the patient group except for significant sex differences seen with higher prevalence of male smokers (47.6% vs. 6,8%; p<0.001) and in distances reached in the 6-minute walking test (352m ± 97m vs. 254m ± 142m, p=0.017). According to the WHO classification, group 2 PH was predominant (46%), followed by group 1 (31%), group 3 (22%) and group 5 (3%). 55.4% of patients presented in WHO functional class III or IV and the mean Karnofsky Performance score was 67±17%.

Table 28 : Clinical characteristics of the 65 patients with pulmonary hypertension

	All (n=65)	**Male (n=21)**	**Female (n=44)**	**P-value**
Mean age (years)	43±15	47±14	41±15	0.133
Hypertension	25 (38.5)	9 (48.8)	16 (36.4)	0.972
Ex-smoker Current smoker	7 (12.3) 5 (7.7)	8 (38.1) 2 (9.5)	0 4 (6.8)	**0.001**
Previous or current pulmonary TB	21 (32.3)	7 (33.3)	13 (29.5)	0.536
Body mass index (kg/m^2)	23.7±5.8	24.1±6.5	23.5±5.5	0.690
Heart rate (bpm)	93±19	91.6±10.2	94.7±5.8	0.195
Pulse oximetry at rest (%)	97 (93-98)	97 (93-98)	97 (93-99)	0.156
Systolic BP (mmHg) Diastolic BP (mmHg)	117±22 78±16	123±27 82±19	114±14 77±14	0.186 0.238
WHO functional class III or IV	36 (55.4)	13 (61.9)	23 (52.3)	0.323
Distance walked at 6-minutes walking test (m)	300 (188-360)	350(300-390)	294 (125-345)	**0.017***
Right heart echocardiographic findings				
Right ventricular systolic pressure (mmHg)	61.4 ± 19.8	60.5±24.6	61.8±17.2	0.797
Tricuspid annular plane systolic excursion (mm)	14.9±5	14.7±5.8	15±4.5	0.844
Right ventricle enlargement	56 (86.2)	18 (85.7)	38(86.4)	0.335
Right atrial enlargement	57 (87.7)	19 (90.5)	38(86.7)	0.830

Data are n (%) or mean ± SD; BP, Blood pressure; WHO, World Health Organization; * statistically significant ($p<0.05$).

6.3.2. Prevalence of ECG abnormalities

Compared to the control group, all abnormalities were more frequently observed in our PH cohort. As shown in Figure 30 (right panel), the most prevalent (cohort vs. control) major abnormalities were: pathologic Q wave (47.7% vs. 6.7%) followed by LVH (38.5% vs. 9.8%) and P-pulmonale (36.9% vs. 20.7%). None of the patients had a completely normal ECG as opposed to 15% in the control group. Of minor ECG abnormalities tachycardia (40% vs. 12.6%) and QRS axis ≥ 100° (38.5% vs. 5.3%), were the most prevalent. 58.5% of the PH group vs. 76.5% were in sinus rhythm. Bradycardia (1.5% vs. 4.9%) and RBBB with QRS right axis deviation (1.5% vs. 1.1%) were the least prevalent. ECG minor abnormalities are shown in Figure 30 (left panel). Overall, 32.3% (24.6%) of ECGs in PH group had at least 3 to 4 major (minor) abnormalities vs. 4.2% (0%) in the control group.

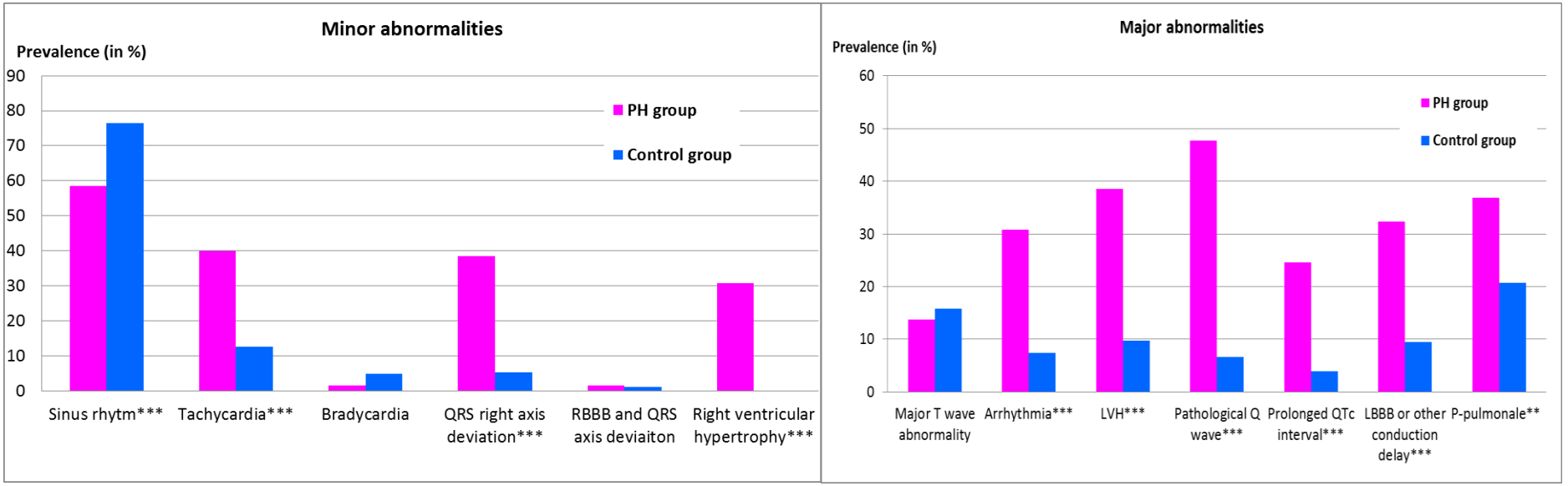

Figure 30: Prevalence of minor (left panel) and major (right panel) ECG abnormalities in 65 patients with PH in the PAPUCO registry compared to 285 controls with normal Doppler echocardiography and right ventricular systolic pressure.

LBBB: left bundle branch block; RBBB: right bundle branch block, QRS right axis deviation = QRS axis > 100°. * p<0.05, ** p<0.01, *** p< 0.001

6.3.3. Predictive values of ECG patterns suggestive of right heart strain for diagnosis of pulmonary hypertension

Table 29 below shows the sensitivity, specificity and positive and negative predictive values for prevalent PH. Sensitivity ranges between 6.2 and 47.7% while specificity ranges between 79.3 and 100%. The negative predictive value ranges between 81.5% and 88.9%. Positive predictive value was lowest at 25% for RBBB and QRS right axis deviation (≥ 100°) and highest at 100% for QRS axis ≥ +100° combined with R/S ratio ≥1 or R in V1 >7mm.

Table 29: Predictive values of ECG patterns suggestive of right heart strain (Right Ventricular Hypertrophy or Right Atrial Enlargement) for diagnosis of PH in the PAPUCO registry

ECG criterion	Sensitivity	Specificity	Positive predictive values	Negative predictive values
QRS axis ≥ 100°	38.46%	94.74%	62.50%	87.10%
R/S ratio >1 or RV_1 >7 mm	47.69%	95.79%	72.09%	88.93%
Definite RVH: QRS axis ≥ +100°; and R/S ratio ≥1 or R in V_1 >7mm	30.77%	100.00%	100.00%	86.36%
Right bundle branch block and QRS right axis deviation (≥ 100°)	1.54%	98.95%	25.00%	81.50%
P > 2,.mm in lead II or >1.5mm in lead V1/V2, unchanged duration	36.92%	79.30%	28.92%	84.64%

RVH, Right ventricular hypertrophy

6.3.4. Predictive values of ECG patterns of right heart strain for diagnosis of indirect signs of PH (echocardiographic right ventricular (atrial) enlargement) in patients with PH

The sensitivity for predicting right ventricular (atrial) enlargement (RV(A)E) were relatively similar for all parameters ranging from 2.1 to 56.3 and 2.6 to 57.9 respectively (Table 30). The specificity was higher for both RVE and RAE for all parameters (all above 60%). Positive predictive value was shown to be higher for RVE than for RAE, where all parameters had higher values than 90%. Negative predictive values were higher for RAE than for RVH, but for both it was relatively low (all below 50%).

Table 30: Predictive values of ECG patterns of right heart strain for diagnosis of indirect signs of pulmonary hypertension (Right Ventricular (Atrial) Enlargement) in patients with PH from the PAPUCO registry

ECG criterion	Sensitivity		Specificity		Positive predictive values		Negative predictive values	
	RVE	RAE	RVE	RAE	RVE	RAE	RVE	RAE
QRS axis ≥ 100°	45.83%	47.37%	85.71%	73.91%	91.67%	75.00%	31.58%	45.95%
R/S ratio >1 or RV1>7 mm	56.25%	57.89%	78.57%	65.22%	90.00%	73.33%	34.38%	48.39%
Definite RVH: QRS axis ≥ +100°; and R/S ratio ≥1 or R in V_1 >7mm	37.50%	42.11%	92.86%	86.96%	94.74%	84.21%	30.23%	47.62%
Right bundle branch block and QRS right axis deviation (≥100°)	2.08%	2.63%	100.00%	100.00%	100.00%	100.00%	22.95%	38.33%
P > 2 mm in lead II or >1.5 mm in lead V1/V2, unchanged duration	45.83%	39.47%	85.71%	60.87%	91.67%	62.50%	31.58%	37.84%

RV(A)E: Right ventricular (atrial) enlargement

6.4. Discussion

The main findings of the present study are that (i) ECG abnormalities are very common among Africans with PH but not specific; ii) ECG abnormalities relating to right heart strain are less frequently observed; iii) ECG patterns focusing on the R and S amplitude in V1 and right axis deviation with QRS axis deviation > 110° have good predictive values for PH. Previous studies in patients with heart failure in SSA have also described high prevalence rates and poor specificity of ECG abnormalities (177, 178). In several low-income-countries, 12-leads ECG is still not widely available in most rural areas, but remains the only cardiac test affordable for rural and poor population (179). The ECG fulfils basic criteria of a good screening test: it is rapid, is non-invasive, requires minimal technical expertise to perform, and is inexpensive. Even though its performance and reliable interpretation require training, skills can easily be acquired and are usually incorporated in basic training of medical students. Performance can be incorporated in the training of nurses. Contrariwise, Doppler echocardiography is often unavailable in resource-constrained settings, remains very expensive and requires much more specialized training competency for performance and interpretation. In this context, the validation of ECG as a good clinical tool with acceptable predictive values for significant PH, could be a relevant and feasible solution to guide the clinicians in selecting appropriate patients for further testing.

6.4.1. Prevalence of ECG abnormalities in Pulmonary Hypertension

ECG abnormalities were very common in this cohort, but taken individually, none exceeded 50%. The fact that all ECGs in this study revealed at least one minor abnormality could be due to the following reasons i) the presence of structural cardiac abnormalities since 46% of patients had left heart disease and ii) the presence of comorbidities like hypertension (38.5%). These findings suggest, as previously reported in SSA populations, that a normal ECG is rare in patients with suspected heart disease (177, 178). In a population of PH predominately due to chronic lung disease, Al-Naamani et al (180) reported that ECG patterns suggestive of RVH were rare (<7%). In idiopathic PAH, Kopec et al (181) reported that the prevalence of RVH varied markedly across the analysed criteria, ranging from 0 to 22. In our study, ECG patterns

suggestive of right heart strain range from 13.9 vs. 15.8% for T wave abnormalities to 38.7 vs. 5.3% for QRS axis deviation in the PH vs. control group respectively. Differences in prevalence of ECG abnormalities between studies could be explained by different population characteristics but also the late presentation of our patients. This is particularly valid for P-pulmonale where high prevalence could be because, as suggested in a previous study (180), it only occurs with atrial involvement in more advanced disease. Indeed, this is supported by the fact that in the overall PAPUCO cohort as described in Chapter 3, 37% of patients presented with right heart failure, the only predictor of mortality in our overall cohort of PH. In the Heart of Soweto study, up to 28% of 2505 urban Africans presenting with de novo heart disease had right heart failure (110). We cannot overemphasize the importance of early diagnosis. However, higher prevalence rates of ECG patterns of right heart strain in our control group would tend to suggest that the majority of ECG abnormalities are non-specific.

6.4.2. Predictive value of ECG abnormalities

Investigating markers of early diagnosis of PH is largely justified by: 1) the current unacceptable time interval (27 months) (69) between the onset of symptoms and eventual diagnosis; 2) its evolution to right ventricular failure and death when diagnosed late or managed inappropriately. Although neglected for years, the role of standard ECG as a marker of PH or RV hypertrophy or dilation has received recent attention (170, 173, 174, 180, 181). For direct diagnosis of PH, our study showed a poor sensitivity (from 1.5 to 47.7%) and high specificity (greater than 80%) for all the studied ECG criteria and good positive and negative predictive value for ECG patterns focussing on R or S amplitude. For prediction of indirect signs of PH like right ventricular(atrial) enlargement (RV(A)E), criteria focussing on R or S amplitude once again showed poor sensitivity, good specificity to RVE and good predictive value for both RVE and RAE. Overall, the negative predictive value was poor. QRS axis ≥ 100° demonstrated a good positive predictive value as a direct indication of possible PH. The classical P-pulmonale had poor performance for predicting both RVE and RAE. That ECG criteria focusing on R wave in V1/V2 performed better is not surprising because these leads are closer to the right ventricle. In 282 patients with PH (defined as RVSP>30 mmHg), Al-Naamani et al (180) also reported a best performance to prediction of PH, for ECG patterns focusing on the R and S amplitudes and right axis deviation, with very poor prevalence and

predictive value of P-pulmonale for PH. Other studies of the predictive value of ECG in PH are usually single centre and small sample size studies that have also focused on a specific group or subgroup of PH. In 23 patients with scleroderma, Wokhlu et al (182) reported better performance for P-wave amplitude in lead II, thus having a 73% sensitivity and 67% specificity for the presence or absence of elevated mean pulmonary artery pressure. In 23 patients with idiopathic pulmonary arterial hypertension, Kopec et al (181) reported that only a few of the recommended ECG criteria proved to be useful in the diagnosis of RV hypertrophy or dilation including the ECG voltage criteria based on R wave amplitude in V1 and ventricular activation time in V1 were useful for differentiating between patients with and without RVH. A very high overall sensitivity of the ECG with respect to PH has been reported by Bossone et al (183) with only six (9%) out of 64 consecutive patients having a normal ECG. Differences with our relatively low sensitivity could again be due to different populations of PH groups, but it shall also be noted that the high sensitivity in the study by Bossone et al was achieved only if ECG was interpreted by a cardiologist who were aware of all other patients' basic clinic data. Bonderman et al (184) also described a relatively high sensitivity of 77% for ECG criteria for suspecting pre-capillary PH. Interestingly, these authors tested a unique model of both abnormalities focusing on R or S in V1 and repolarisation patterns from V1 to V3. However, it's only by combining ECG and NT-proBNP in addition to Doppler echocardiography that their model could suffice to predict significant pre-capillary PH at a level of sensitivity of 100% and specificity of 19.3%. This highlights the need of further tests to improve the suspicion index for PH in presence of ECG abnormalities.

6.4.3. Strengths and limitations

Among the limitations described in chapter 2, 3 and 4 in this thesis, the absence of confirmation of PH diagnosis using right heart catheterization applies here. Second, we did not explore the performance of some individual criteria like RV1≥7 mm, RV5≤5 mm, R in lead I≤1 mm, S in V1≤2 mm, R/SV1≥1, QRSaxis≥110° but rather their combinations. This is unlikely to affect the predictive value of the criteria evaluated in our study, however some of these individual indices have been previously shown to have good positive predictive value (181). Finally, the heterogeneity of our study population as well as the limited sample size is a concern and could limit generalizability of our findings. Beyond these limitations, late

presentation of patients with PH worldwide and particularly in the PAPUCO registry and SSA at large as described in Chapter 3 is absolutely unacceptable and needs to be addressed with simple and available tools.

6.5. Conclusion

ECG abnormalities are very frequent in people with PH in SSA, although the value of most of these abnormalities is largely limited. When present, some abnormalities like right axis deviation and R/S ratio in $V_1 > 1$ or R wave in $V_1 > 7$mm should trigger further investigation with echocardiography. Innovative measures in electrocardiography are required for improving diagnosis of PH in SSA. This could include studies combining ECG with Echocardiography, clinical criteria and cardiac biomarkers to better define criteria to early diagnosis of PH without exposing patients to unnecessary and costly right heart catheterization in limited resources settings.

Chapter 7. Prognostic Significance of ECG Abnormalities for Mortality Risk in Acute Heart Failure: Insight from the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF)

7.1. Introduction

As previously described in the background section of this thesis, our knowledge of the contribution of ECG in the management of pulmonary hypertension (PH) is limited and derives much from western studies either on heart failure (HF) or on pulmonary arterial hypertension (PAH). Yet, it is recommended by several international guidelines that ECG should be included in the initial diagnostic process of all patients with HF (54, 185). HF is the main etiology of PH worldwide. ECG is a simple, relatively cheap and available test that can be used in exploring all patients with suspected HF regardless of the presence of PH. Considering the rising burden of HF in SSA (115, 186), we investigated the predictive utility of 12-lead ECG abnormalities among Africans with acute heart failure (HF) using data from the sub-Saharan Africa Survey of Heart Failure. The PAPUCO data were not enough to investigate this question, and due to different inclusion criteria and temporal difference in recruitments, we used only the THESUS-HF data.

Our result showed that a normal ECG is very rare among Africans with acute HF. Also, some ECG findings had prognostic value for mortality risk, although most of them were nonspecific and added little to the risk stratification of these patients.

We concluded that ECG may add to the immediate diagnosis of patients presenting with dyspnea in the emergency room in SSA settings and can therefore be used to screen patients needing a more expensive, more specialized and less available test like echocardiography.

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Prognostic Significance of ECG Abnormalities for Mortality Risk in Acute Heart Failure: Insight From the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF)

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ABSTRACT

Objective: The aim of this study was to assess the predictive utility of 12-lead electrocardiogram (ECG) abnormalities among Africans with acute heart failure (HF).

Methods and Results: We used the Sub-Saharan Africa Survey of Heart Failure, a multicenter prospective cohort study of 1,006 acute HF patients, and regression models to relate baseline ECG findings to all-cause mortality and readmission during a 6-month follow-up period. Of 814 ECGs available, 523 (49.0% male) were obtained within 15 days of admission, among which 97.7% showed abnormalities. Mean age was 52.0 years and median follow-up was 180 days, with 77 deaths (Kaplan-Meier 17.5%) through day 180 and 63 patients with death or readmission to day 60. QRS width, QT duration, bundle branch block, and ischemic changes were not associated with outcomes. Increasing ventricular rate was associated with increasing risk of both outcomes (hazard ratio [HR] 1.07 per 5 beats/min increase for 60-day death or readmission, 95% confidence interval [CI] 1.02–1.12; P = .0047), and the presence of sinus rhythm was associated with lower risk (HR 0.58, 95% CI 0.34–0.97; P = .0385). There was a strong association between survival and heart rate in patients in sinus rhythm, with heart rate ≥119 beats/min conveying the worst mortality risk.

Conclusions: ECG abnormalities are almost universal among Africans with acute HF, which may add to the immediate diagnosis of patients presenting with dyspnea. Although some ECG findings have prognostic value for risk of adverse outcomes, most of them are nonspecific and add little to the risk stratification of these patients. (J Cardiac Fail 2014;20:45–52)

Key Words: Africa, heart failure, electrocardiogram, outcome, prognosis.

The 12-lead electrocardiogram (ECG) represents a widely available test, relatively inexpensive, simple to perform, and yields an instant result. It is objective and reproducible. ECG is recommended by the American Heart Association and European Society of Cardiology as initial test in patients with heart failure (HF).[1,2] Indeed, most patients with HF due to systolic dysfunction have a significant abnormality on ECG.[3]

However, the grade and spectrum of ECG abnormalities may differ by HF etiology and possibly other factors, such

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as ethnicity.[4] The current knowledge on 12-lead ECG abnormalities in HF is largely derived from North American and European cohorts (predominantly white men).[4] Sliwa et al recently reported findings from a large study of electrocardiographic findings among heart disease–free Africans,[5] showing that some of the suggested ECG criteria may be less applicable in this population; eg, up to 13% of the studied population presented with significant Q waves in the absence of myocardial ischemia.

To our knowledge, the diagnostic and prognostic utility of the ECG in Africans with acute HF was not been reported. The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF)[6] prospectively collected clinical data in an African cohort of patients with HF during admission and after follow-up, and thus gives the first unique opportunity to study the utility of ECG in patients admitted with HF in this part of the world.

Methods

Study Design and Clinical Setting

THESUS-HF was a prospective, multicenter, international observational survey conducted in 12 cardiology centers from 9 countries in the southern, eastern, central, and western regions of sub-Saharan Africa, as described in detail elsewhere.[6] Ethical approval was obtained from the Ethical Review Boards of the participating institutions, and the study conformed to the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients admitted with dyspnea as the main complaint to each of the participating centers from July 2007 to June 2010 were screened for inclusion in the study. Patients ≥12 years of age with clinical signs and symptoms consistent with congestive heart failure (ie, pedal edema, elevated jugular venous pressure, pulmonary congestion, and tender hepatomegaly) and patients that were prepared to continue follow-up, including visits over 6 months, were included. Exclusion criteria included acute ST-segment elevation myocardial infarction (but not chronic ischemic cardiomyopathy), severe known renal failure (patients on dialysis or creatinine >4 mg/dL), nephrotic syndrome, and chronic liver disease or other cause of hypoalbuminemia. Written informed consent was obtained from each subject.

Data Collection

A comprehensive range of clinical data were collected on a standardized case report form. This included demographic data and detailed medical history. A detailed echocardiographic assessment of ventricular contractility, valvular structure and function, and regional wall abnormalities was performed. All echocardiographic procedures were undertaken by trained physicians and measurements made according to the American Society of Echocardiography guidelines.[7]

Laboratory evaluations provided by the local institutions and intravenous and oral medications were recorded at admission and days 1, 2, and 7 (or at discharge if earlier). Vital signs (blood pressure, heart rate, respiratory rate, and temperature) and signs and symptoms of HF (including oxygen saturation, intensity of edema and rales, body weight, and levels of orthopnea) were assessed at the same time points. Changes in dyspnea and well-being relative to admission were assessed on days 1, 2, and 7 (or at discharge if earlier). Investigators provided the final diagnosis of HF and its cause. Cardiomyopathy was classified according to the position statement from the European Society of Cardiology.[8] Hypertensive HF, right-sided HF, and ischemic HF were defined by standard criteria.[9]

Study Outcome

Subjects who were discharged after admission were evaluated at 1 and 6 months. At these time points, patients were evaluated for signs and symptoms of HF, laboratory evaluations were performed, and oral medications were recorded. Readmissions and death, with reasons and cause, respectively, through 6 months of follow-up were collected.

ECG Data Acquisition and Interpretation

A 12-lead ECG was performed within 15 days of admission. All ECGs were read centrally by Momentum Research by one cardiologist (O.M.) and reviewed another (G.C.). ECGs were analyzed for conduction or rhythm disturbances, evidence of myocardial ischemia/infarction, or hypertrophy. The following parameters were entered in the database registry together with other clinical data: heart rate; length of QRS, QT, and QTc intervals; type of rhythm (sinus rhythm, atrial fibrillation/flutter, other supraventricular tachycardia, ventricular tachycardia, junctional rhythm, ventricular pacing, 1st-, 2nd-, or 3rd-degree atrioventricular block); Q wave compatible with myocardial infarction as well as all other forms of Q waves; and ST-T segment changes. ST-T segment changes were noted as ST-segment elevation at the J point in 2 contiguous leads of 0.2 mV in men or 0.15 mV in women in leads V2–V3 or 0.1 mV in other leads, as ST-segment depression of horizontal or down-sloping depression of 0.05 mV in 2 contiguous leads, as nonspecific ST-T abnormality where changes did not meet the above criteria for ST-segment elevation or depression, or as changes due to bundle branch block. Left ventricular hypertrophy (LVH) was determined with the use of the Sokolow-Lyon index (SV1 + RV5/6 > 35 mm), and all of other described ECG parameters were defined and analyzed according to the standard international criteria and definitions.[10,11] All ECG abnormalities were classified into major and minor with the use of the Minnesota code classification system which allows a systematic approach and facilitate an easy appreciation of the prognostic value of ECG findings for total cardiovascular disease.[12]

Statistical Analyses

All data were processed at the central coordinating center at Momentum Research, Durham, North Carolina, USA. Data were analyzed with the use of SAS version 9.2 (SAS Institute, Cary, North Carolina). Summary statistics (mean, SD, median, and 25th–75th percentiles) are provided for continuous variables and frequencies for categoric variables. Some parameters could not be estimated or interpreted by the central reader from the ECG provided. These were treated as missing in the analyses.

The associations of ECG findings with the composite end point of all-cause death or readmission to 60 days and all-cause death to day 180 were evaluated in those subjects with ECGs administered within 15 days of the admission. Univariable and multivariable Cox regression models were constructed considering the time from admission to the first event; times for patients without the

event of interest were censored at the earlier of the last date the patient was known to be alive or the period of interest. Unadjusted Kaplan-Meier survival estimates are presented in the figures.

Multivariable models were constructed from ECG parameters with values available for sufficient subjects. None of the associations between continuous ECG predictors and each outcome was found to be significantly nonlinear, as assessed by examining the significance of the nonlinear terms of restricted cubic splines (RCSs) with 4 "knots." Multivariable models were adjusted for clinical covariates included in multivariable prognostic models in the overall THESUS-HF registry.[6] For the outcome all-cause death or readmission to 60 days, these included history of hyperlipidemia, malignancy, or cor pulmonale, systolic BP, left ventricular ejection fraction, oxygen saturation, rales, blood urea nitrogen, and region. For the outcome all-cause death to day 180, clinical covariates included sex, history of malignancy, cor pulmonale, smoking, or human immunodeficiency virus, systolic blood pressure (BP), heart rate, oxygen saturation, orthopnea, rales, edema, creatinine, and hemoglobin. The ECG parameters QRS duration, QT, QTc, ventricular rate, sinus rhythm, atrial fibrillation/flutter, bundle branch block, left ventricular hypertrophy, T-wave inversion in ≥2 contiguous leads, ST-segment depression ≥1 mm, ST-segment elevation ≥1 mm, nonspecific ST-T changes, isolated pathologic Q waves and Q waves compatible with myocardial infarction (MI) were then added to the multivariable models to see if any had a significant association after adjusting for the clinical covariates.

Approximately 40% of subjects were missing ≥1 of the predictors. Multiple imputations with the use of 7 imputed datasets and assumption of multivariate normality were used to handle missing values. The Rubin algorithm was used for averaging parameter estimates across the imputed datasets. Backward selection of the ECG parameters was performed for each imputed dataset, with predictors with P ! .1 kept in the model. ECG parameters that remained in a majority (≥4) of the models were then included in the final model. c-Statistics are reported for the models with and without the ECG parameters to examine the change in model discrimination with the addition of ECG information.

Results

Of the 1,006 patients enrolled in the THESUS-HF study, 813 patients had an available 12-lead ECG, 523 of which were obtained within 15 days of admission and were included in the analyses.[6] Characteristics of these patients were similar to the overall study population (Supplementary Table 1). The majority of included patients were enrolled in Nigeria (32.1%), Uganda (21.0%), and South Africa (18.9%). Table 1 depicts the baseline characteristics of the 523 subjects (49% male, overall mean age 52 ± 18.4 years) included in the analysis. The etiologies of HF were dominated by hypertension (43.2%), idiopathic dilated cardiomyopathy (21.0%), rheumatic heart disease (17.2%), and ischemic heart disease (7.7%).

Table 1. Baseline Characteristics for Subjects With an Electrocardiogram Within 15 Days of Admission (n = 523)

Age, y	52.0 ± 18.4
Gender, male	256 (49.0%)
Systolic blood pressure, mm Hg	132.9 ± 34.3
Heart rate, beats/min	105.1 ± 21.9
O_2 saturation, %	93.6 ± 7.4
Ejection fraction, %	39.9 ± 16.5
Rales (2/3 vs 0/1)	255 (58.4%)
Orthopnea (2/3 vs 0/1)	388 (89.2%)
Edema (2/3 vs 0/1)	328 (63.7%)
Medical history	
Diabetes mellitus	55 (10.5%)
Hypertension	291 (55.8%)
Hyperlipidemia	44 (8.6%)
Malignancy	8 (1.5%)
Cor pulmonale	38 (7.3%)
Smoking	45 (8.7%)
HIV positive	45 (8.8%)
Etiology of heart failure	
Hypertensive CMP	226 (43.2%)
Idiopathic dilated CMP	110 (21.0%)
Rheumatic heart disease	90 (17.2%)
Ischemic heart disease	40 (7.7%)
Peripartum cardiomyopathy	33 (6.3%)
Pericardial effusion/tamponade	29 (5.5%)
HIV CMP	18 (3.4%)
Endomyocardial fibroelastosis	10 (1.9%)
Laboratory values	
Creatinine, mg/dL	1.43 ± 1.09
Hemoglobin, g/dL	12.4 ± 2.4
eGFR, mL min^{-1} 1.73 m^{-2}	81.7 ± 49.1
BUN, mg/dL	33.3 ± 33.5
Electrocardiographic parameters	
QRS duration, ms	73.9 ± 26.7
QT duration, ms	348.3 ± 52.3
QTc, ms	274.4 ± 71.3
Ventricular rate, beats/min	104.1 ± 26.0
Sinus rhythm	392 (75.1%)
Atrial fibrillation/flutter Left	121 (23.6%)
bundle branch block Right	42 (8.1%)
bundle branch block Left	26 (5.0%)
ventricular hypertrophy	158 (30.6%)
Other electrocardiographic abnormalities	
T-wave inversion in ≥2 contiguous leads	163 (31.2%)
ST-segment depression ≥1 mm	13 (2.5%)
ST-segment elevation ≥1 mm	17 (3.3%)
Nonspecific ST-T changes	124 (23.7%)
Isolated pathologic Q waves	9 (1.7%)
Q-waves compatible with MI	90 (17.2%)

Values are presented as mean ± SD for continuous variables and n (%) presented for categoric data (percentages of nonmissing values). CMP, cardiomyopathy; HIV, human immunodeficiency virus; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; MI, myocardial infarction.

Electrocardiography findings

The mean ventricular rate was 104 beats/min, with a ranged of 40–200 (Supplemental Table 1). Abnormal ECG was detected in 511 out of 523 patients (97.7%). Figure 1 shows the ECG abnormalities in these patients, with major alterations similar in men and women. The distribution of subtypes of minor abnormalities in men and women is depicted in Figure 2.

ECG Abnormalities and Morbidity and Mortality Risks

Patients included in the analyses were followed for a median of 180 days. There were 77 deaths to day 180, with a Kaplan-Meier event rate of 17.5%. There were 63 patients with a death or readmission to day 60, for a rate of 13.5%. Eighty subjects (15.3%) died without completing a 6-month assessment, 261 (49.9%) had a 6-month assessment, and 156 (29.8%) had a last known

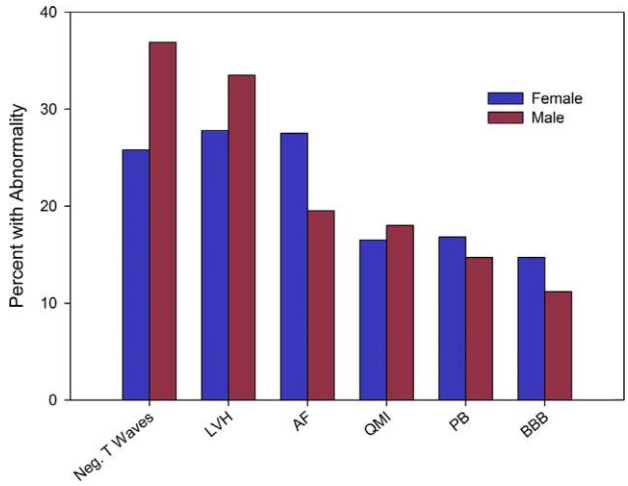

Fig. 1. Major electrocardiographic abnormalities in male and female patients. LVH, left ventricular hypertrophy; AF, atrial fibrillation/flutter; QMI, Q wave compatible with myocardial infarction; PB, premature beats; BBB, bundle branch block.

date alive. The remaining 26 patients (5.0%) were considered to be lost to follow-up.

Without adjustment, QRS width and QT duration were not associated with either the composite outcome of death or readmission through 60 days or death through 180 days (Tables 2 and 3). Bundle branch block and ischemic changes were not independently significantly associated with either outcome.

Corrected QT intervals were calculated for all patients, and after dividing patients into male and female cohorts only 7 out of 254 male patients (2.8%) had a borderline to abnormal QTc (O430 ms) and only 6 out of 267 female patients (2.2%) had a borderline to abnormal QTc (O450 ms).

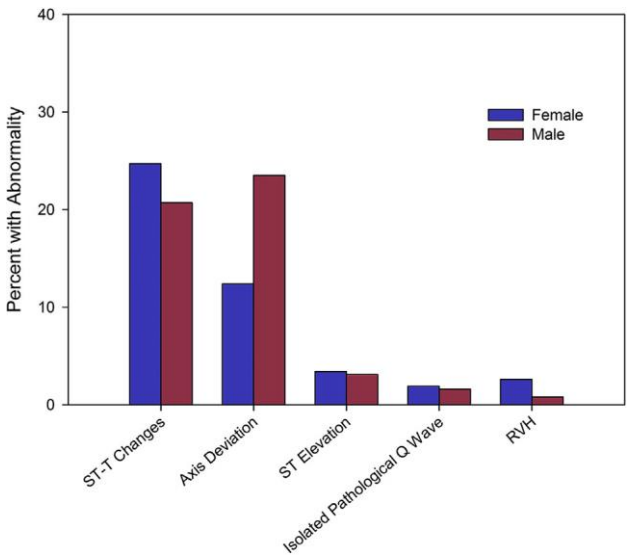

Fig. 2. Minor electrocardiographic abnormalities in male and female patients. RVH, right ventricular hypertrophy.

Increasing ventricular rate was associated with increasing risk of both outcomes, whereas the presence of sinus rhythm was associated with lower risk (Fig. 3). Heart rate analysis when patients were divided into quartiles based on the heart rate showed an association with survival probability. Further analysis based on the heart rate and sinus rhythm/atrial fibrillation showed strong association between survival and heart rate specifically in patients in sinus rhythm. Patients in sinus rhythm with heart rate of O119 beats/min fared the worst (Fig. 3).

After multivariable adjustment, lack of sinus rhythm and Q waves associated with MI were the only ECG variables associated (P ! .10) with the risk of death or readmission within 60 days (Table 2) or death within 180 days (Table 3). The addition of these ECG parameters did not improve the multivariable models' discrimination (the ability to correctly classify patients with versus without an event) over a model including clinical and laboratory characteristics for either 60-day readmission or death (c-statistic 0.74, 95% CI 0.67e0.80, versus 0.70, 95% CI 0.65e0.75) or 180-day mortality (c-statistic 0.77, 95% CI 0.72e0.82, versus 0.72, 95 CI 0.68e0.75).[13]

Discussion

In this large cohort study of acute HF in 9 sub-Saharan African countries, we found a high prevalence (97.7%) of ECG abnormalities. Also, our analysis indicated that some of these abnormalities are associated with a higher risk for adverse outcome in these patients. The predominant abnormalities include increased heart rate, lack of sinus rhythm, and Q waves, all of which were associated with a higher risk of adverse outcomes. This study confirms the previously reported high prevalence rates of abnormal ECG[3] and the fact that some of these findings are associated with more adverse outcome.[14] However, when adjusted for additional baseline characteristics, ECG findings did not improve the ability of the model to predict adverse outcome and therefore added little to the risk stratification of patients with AHF.

The high prevalence of ECG abnormalities is probably because a significant number of these patients suffered from structural cardiac abnormalities such as reduced EF and valvular diseases as well as comorbidities such as hypertension (56%) and diabetes mellitus (DM) (11%). This finding would tend to suggest, as reported elsewhere, that a normal ECG is rare in patients with suspected HF and is clinically useful in confirming the presence of heart disease without a need to resort to other tests, such as B-type natriuretic peptide. The almost universal presence of ECG abnormality implies that a patient with signs and symptoms of acute HF and a normal ECG has a noncardiac cause of the presentation until proven otherwise. Interestingly, and consistent with the main results of the THESUS-HF study, only 90 patients (17.2%) were found to have Q waves compatible with MI, which, again, is in line with earlier studies showing that ischemic heart disease is an uncommon cause of acute HF in sub-Saharan Africa.[6,15e18]

Table 2. Univariable and Multivariable Models of All-Cause Death or Readmission Through Day 60

Baseline Characteristic	HR for Change of	Univariable Models HR (95% CI)	P Value	Full Model HR (95% CI)	P Value	Multivariable Model HR (95% CI)	P Value
History of hyperlipidemia	Yes/No	0.32 (0.07–1.44)	.1381	0.38 (0.08–1.91)	.2407	0.32 (0.07–1.59)	.1642
History of malignancy	Yes/No	5.79 (2.11–15.87)	.0007	7.72 (2.54–23.48)	.0003	6.76 (2.30–19.87)	.0005
History of cor pulmonale	Yes/No	2.60 (1.31–5.14)	.0062	1.76 (0.82–3.79)	.1453	1.64 (0.78–3.46)	.1937
Systolic blood pressure	10	0.93 (0.86–1.00)	.0634	0.95 (0.87–1.04)	.2621	0.96 (0.88–1.04)	.2831
Ejection fraction	50 vs 28	0.78 (0.55–1.12)	.4099	0.79 (0.52–1.20)	.5261	0.81 (0.55–1.21)	.6129
O_2 saturation	5	0.89 (0.77, 1.01)	.0798	0.86 (0.73–1.00)	.0528	0.88 (0.75–1.02)	.0929
Rales	(2/3 vs 0/1)	1.81 (1.00–3.28)	.0499	1.73 (0.85–3.52)	.1329	1.78 (0.88–3.59)	.1095
Laboratory tests							
BUN (log 2)	Doubling (South	1.37 (1.10–1.72)	.0059	1.46 (1.12–1.91)	.0053	1.42 (1.10–1.85)	.0077
Region*	vs West) (East	1.66 (0.98–2.82)	.0602	2.94 (1.56–5.55)	.0009	2.77 (1.49–5.17)	.0014
Region	vs West)	0.50 (0.22–1.14)	.0993	0.89 (0.35–2.30)	.8129	0.83 (0.33–2.05)	.6825
Electrocardiographic parameters							
QRS duration	10	0.99 (0.90–1.09)	.8998	0.97 (0.85–1.10)	.6453		
QT	20	0.94 (0.85–1.03)	.2076	1.07 (0.83–1.37)	.6189		
QTc	10	0.97 (0.93–1.01)	.1002	0.96 (0.88–1.05)	.3558		
Ventricular rate, beats/min	5	1.07 (1.02–1.12)	.0047				
Sinus rhythm	Yes/No	0.58 (0.34–0.97)	.0385	0.55 (0.30–1.01)	.0557	0.52 (0.30–0.90)	.0200
Atrial fibrillation/flutter Left	Yes/No	1.59 (0.92–2.75)	.0941				
bundle branch block Right	Yes/No	1.55 (0.71–3.41)	.2726	2.27 (0.77–6.65)	.1356	1.89 (0.82–4.32)	.1335
bundle branch block Left	Yes/No	1.31 (0.48–3.60)	.5974	1.82 (0.53–6.22)	.3376		
ventricular hypertrophy	Yes/No	0.54 (0.29–1.02)	.0578	0.82 (0.40–1.68)	.5820		
Other electrocardiographic abnormalities							
T-wave inversion in ≥2 contiguous leads	Yes/No	0.71 (0.40–1.26)	.2399	1.18 (0.58–2.38)	.6453		
ST-segment depression ≥1 mm	Yes/No	1.29 (0.32–5.29)	.7206	2.72 (0.58–12.72)	.2027		
ST-segment elevation ≥1 mm	Yes/No	0.91 (0.22–3.72)	.8937	0.93 (0.21–4.16)	.9240		
Nonspecific ST-T changes	Yes/No	0.95 (0.53–1.73)	.8744	0.74 (0.36–1.53)	.4210		
Isolated pathologic Q waves	Yes/No	2.36 (0.58–9.63)	.2341	2.03 (0.44–9.26)	.3621		
Q waves compatible with MI	Yes/No	1.41 (0.78–2.56)	.2561	1.74 (0.85–3.56)	.1297	1.86 (0.97–3.54)	.0608
c-Statistic				0.7448 (0.6782–0.8113)		0.7387 (0.6749–0.8024)	

MI, myocardial infarction.
*Regions: East: Ethiopia, Kenya, Sudan, and Uganda; South: Mozambique and South Africa; West: Cameroon, Nigeria, and Senegal.

Most other ECG findings were nonspecific. These observations are in agreement with the recent study that was conducted by Khan et al[3] drawing from the Euro Heart Failure survey of 11,327 patients admitted for acute HF suggesting that most ECG findings in these patients are nonspecific and that ECG criteria alone were not accurate for the diagnosis or exclusion of specific cardiac abnormalities in patients with acute HF.

Similarly, the results of the present study suggest that although some ECG variables (especially rate and rhythm and the presence Q waves) are associated with worse outcomes, these factors do not increase the predictive value of the models for readmission or mortality. Untreated patients with HF usually exhibit a high heart rate that results from hyperadrenergia; however, we can not rule out that the association of higher heart rate with mortality may indeed be due to more severe neurohormonal activation in these patients.[19] The rate of left bundle branch block (LBBB) in our study was low (8%), compared with 16%–22% in other populations admitted for HF in European countries.[20,21] Moreover, LBBB was not associated with increased mortality, in contrast to associations reported in the European population; differences between populations with different age and etiology of HF (ie, less ischemic cardiomyopathy, more hypertensive and rheumatic heart disease) might account for these findings. Similar results were reported by Hebert et al, in Hispanics with systolic HF.[22] Even though they found higher prevalence of paced rhythm, LBBB, and abnormal QT intervals, in univariate and multivariate analysis corrected for other characteristics (age, sex, coronary artery disease, hypertension, ejection fraction, medications) ECG findings added little prognostic information. Therefore, it seems that although ECG is an important assessment that should be performed routinely in patients with acute HF, its value lies mostly in excluding some specific causes of acute HF such as MI or life-threatening arrhythmias. Other electrocardiographic findings do not substantially help in the risk stratification of patients with acute HF.

Although found previously to be independently associated with adverse outcomes in 2 recent studies in 872 patients with preserved systolic function[23] and in 4,133 patients enrolled in EVEREST trial[24] which included acute HF patients with ejection fraction #40% QRS duration was nonsignificantly associated with adverse outcome in the present study. Regarding QTc abnormalities, Kolo

Table 3. Univariable and Multivariable Models of All-Cause Death Through Day 180

Baseline Characteristic	HR for Change of	Univariable Models HR (95% CI)	P Value	Full Model HR (95% CI)	P Value	Multivariable Model HR (95% CI)	P Value
Male sex	Yes/No	1.05 (0.67–1.64)	.8454	1.14 (0.68–1.91)	.6209	1.04 (0.63–1.72)	.8657
History of malignancy	Yes/No	6.05 (2.21–16.59)	.0005	5.16 (1.69–15.79)	.0041	5.43 (1.83–16.08)	.0023
History of cor pulmonale	Yes/No	2.71 (1.45–5.05)	.0018	2.11 (1.03–4.32)	.0414	2.09 (1.04–4.23)	.0395
History of smoking	Yes/No	1.12 (0.51–2.44)	.7842	1.35 (0.56–3.25)	.5086	1.31 (0.56–3.08)	.5330
HIV positive	Yes/No	1.30 (0.62–2.72)	.4820	0.92 (0.39–2.19)	.8579	0.99 (0.43–2.27)	.9741
Systolic blood pressure	10	0.85 (0.79–0.92)	.0001	0.87 (0.80–0.95)	.0018	0.88 (0.81–0.95)	.0019
Heart rate	118 vs 90	1.84 (1.22–2.78)	.0016	1.40 (0.88–2.24)	.0582	1.43 (0.93–2.19)	.0483
O_2 saturation	5	0.92 (0.80–1.07)	.2927	0.86 (0.72–1.04)	.1205	0.86 (0.72–1.04)	.1238
Orthopnea	(2/3 vs 0/1)	2.36 (0.83–6.71)	.1063	2.07 (0.64–6.73)	.2237	2.22 (0.72–6.89)	.1657
Rales	(2/3 vs 0/1)	2.03 (1.15–3.59)	.0148	1.27 (0.65–2.50)	.4848	1.37 (0.71–2.65)	.3462
Edema	(2/3 vs 0/1)	2.34 (1.34–4.08)	.0028	2.25 (1.19–4.25)	.0124	2.20 (1.17–4.14)	.0144
Laboratory tests							
Creatinine	1.60 vs 0.90	1.62 (1.11–2.35)	.0412	1.39 (0.96–2.02)	.1698	1.33 (0.93–1.91)	.2640
Hemoglobin	1	0.92 (0.84–1.01)	.0676	0.94 (0.84–1.05)	.2693	0.94 (0.84–1.04)	.2198
Electrocardiographic parameters							
QRS duration	10	0.94 (0.86–1.03)	.1785	0.92 (0.80–1.05)	.2224		
QT	20	0.95 (0.88–1.04)	.2844	1.15 (0.91–1.46)	.2486		
QTc	10	0.98 (0.95–1.01)	.2250	0.97 (0.89–1.06)	.4883		
Ventricular rate, beats/min	5	1.04 (1.00–1.09)	.0572				
Sinus Rhythm	Yes/No	0.56 (0.35–0.90)	.0159	0.64 (0.37–1.13)	.1226	0.61 (0.36–1.02)	.0618
Atrial fibrillation/flutter	Yes/No	1.53 (0.94–2.51)	.0892				
Left bundle branch block	Yes/No	1.00 (0.43–2.32)	.9930	2.18 (0.64–7.39)	.2111		
Right bundle branch block	Yes/No	0.77 (0.24–2.45)	.6565	0.71 (0.18–2.85)	.6324		
Left ventricular hypertrophy	Yes/No	0.52 (0.29–0.93)	.0286	0.71 (0.37–1.35)	.2953		
Other electrocardiographic abnormalities							
T-wave inversion in ≥2 contiguous leads	Yes/No	0.55 (0.31–0.97)	.0393	0.85 (0.44–1.64)	.6259		
ST-segment depression ≥1 mm	Yes/No	0.48 (0.07–3.45)	.4649	1.35 (0.17–10.85)	.7780		
ST-segment elevation ≥1 mm	Yes/No	1.90 (0.77–4.71)	.1646	2.05 (0.74–5.68)	.1659		
Nonspecific ST-T changes	Yes/No	1.45 (0.89–2.37)	.1340	1.62 (0.87–3.03)	.1276	1.57 (0.91–2.72)	.1057
Isolated pathologic Q waves	Yes/No	1.90 (0.47–7.73)	.3719	2.97 (0.65–13.46)	.1587		
Q waves compatible with MI	Yes/No	2.19 (1.34–3.57)	.0017	2.34 (1.23–4.46)	.0098	2.45 (1.39–4.32)	.0020
c-Statistic				0.7729 (0.7198–0.8260)		0.7683 (0.7163–0.8204)	

MI, myocardial infarction.

et al,[25] in a study including 90 Nigerian patients with chronic HF, found QTc to be prolonged in 63% of patients. However, in the present study of patients with acute HF, we found that few patients had QTc prolongation: 7 out of 254 male patients (2.8%) had a borderline to abnormal QTc (≥430 ms) and 6 out of 267 female patients (2.2%) had a borderline to abnormal QTc (≥450 ms).

Taking into consideration that a significant proportion of the patients in our study were hypertensive, we expected to find a substantial prevalence of ECG signs of LVH. However, only 158 patients (30.6%) met the criteria for LVH. Moreover, in disagreement with earlier subanalysis of the CHARM program,[26] where ECG LVH was reported as an independent predictor of worse outcome, in the present study patients with LVH tended to be at decreased risk for both all-cause mortality and readmission through day 60 as well as all-cause mortality through day 180. This finding is unexpected and requires confirmation in further studies; however, it is possible that hypertensive HF has a relatively benign prognosis in Africa.

There are several weaknesses of the present study. First, ECGs were available in only 523 of the 1,006 patients in the THESUS-HF cohort. However, patients with available ECGs had characteristics similar to the rest of the cohort. The second issue is the lack of standardization of the manner in which the ECGs were acquired. Inconsistent placement of ECG electrodes is known to have an effect on ECG voltages which are important in the assessment of cardiac hypertrophy.[27] Third, missing data for other variables may have diluted the associations that were sought in this study. Fourth, owing to no access to cardiac catheterization in a number of centers, we might have missed some cases of HF due to ischemic origin. And finally, we can not rule out the possibility that by recording ECGs at ≤15 days and not absolutely on admission, our study missed some transient ECG abnormalities. These limitations, however, have to be considered in the context of the study setting, where major constraints to high-quality clinical research are still commonplace. The study was conducted in selected specialized centers, and only patients who consented to the study were enrolled; thus, not all patients admitted with AHF are represented and the study's generalizability is somewhat limited. However, we have increased our understanding of the growing importance of chronic cardiovascular disease in this population, who are often thought to suffer much from infectious diseases.

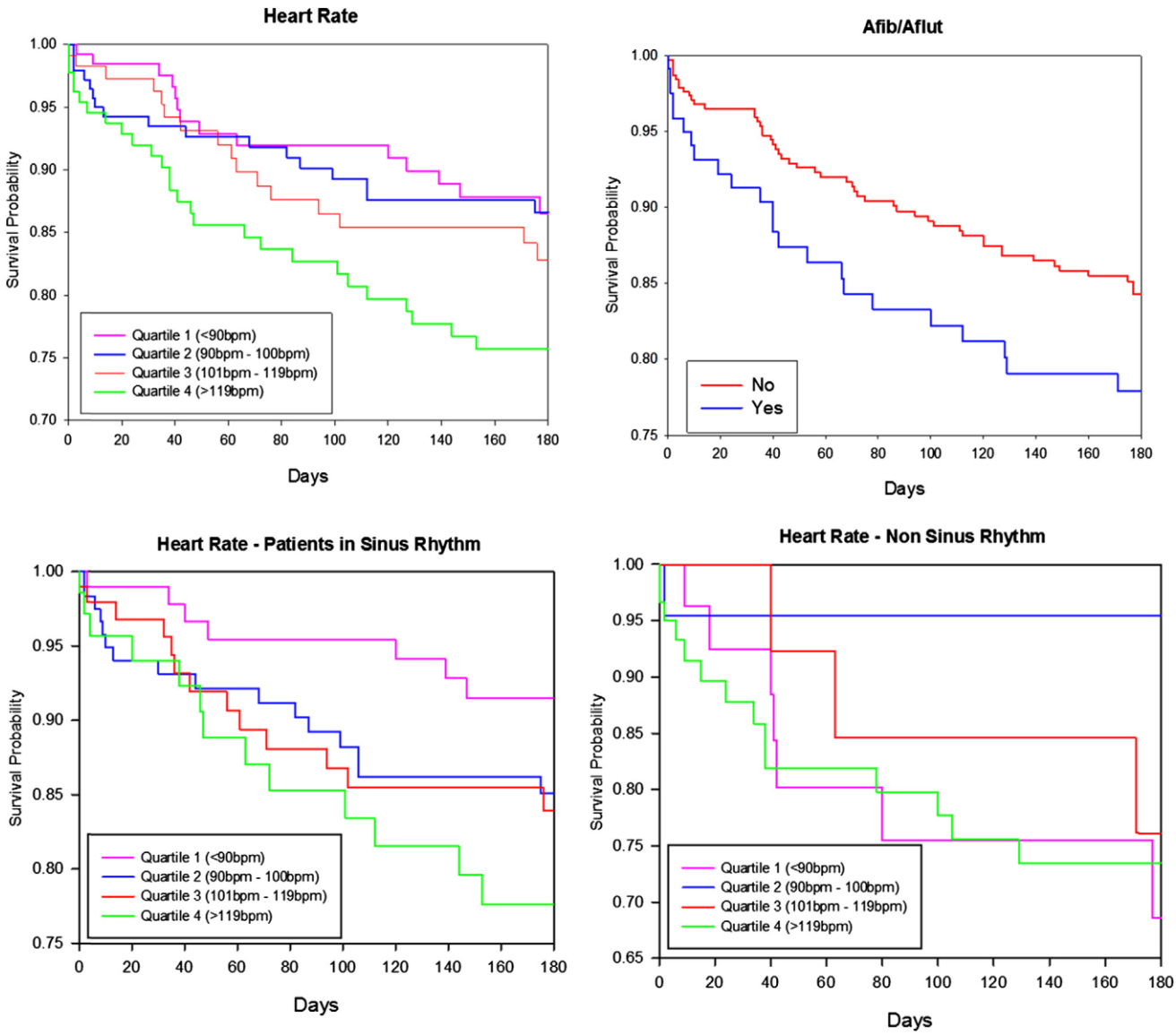

Fig. 3. Kaplan-Meier estimates of 180-day survival according to various electrocardiographic findings within 15 days of admission. Afib/Aflut, atrial fibrillation/flutter.

Conclusion

In African patients admitted for acute HF, ECG abnormalities are present in 98% of cases, and some of these abnormalities (eg, higher heart rate, nonsinus rhythm, presence of Q waves) are associated with higher risk for adverse outcomes. Although ECG should be routinely obtained in patients admitted for acute HF to confirm presence of heart disease and rule out acute ischemia and severe rhythm disorders, for the most part ECG abnormalities in African patients with acute HF are nonspecific and add little to the risk stratification of those patients.

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Disclosures

None

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.cardfail.2013.11.005.

References

1. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA guidelines for

the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:1977e2016.

2. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803e69.
3. Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, et al. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail 2007;9:491e501.
4. Mason JW, Ramseth DJ, Chanter DO, Moon TE, Goodman DB, Mendzelevski B. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. J Electrocardiol 2007;40:228e34.
5. Sliwa K, Lee GA, Carrington MJ, Obel P, Okreglicki A, Stewart S. Redefining the ECG in urban South Africans: electrocardiographic findings in heart disease-free Africans. Int J Cardiol 2012 Jul 13.
6. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. Arch Intern Med 2012;172:1386e94.
7. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685e713.
8. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270e6.
9. Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. Circulation 2008;118:2360e7.
10. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation 2009;119:e241e50.
11. Wagner GS, Macfarlane P, Wellens H, Josephson M, Gorgels A, Mirvis DM, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53:1003e11.
12. de Bacquer D, de Backer G, Kornitzer M, Blackburn H. Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. Heart 1998;80:570e7.
13. Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, et al. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry. Eur Heart J 2013;34:3151e9.
14. Vaclavik J, Spinar J, Vindis D, Vitovec J, Widimsky P, Cihalik C, et al. ECG in patients with acute heart failure can predict in-hospital and long-term mortality. Intern Emerg Med Published online October 6, 2012.
15. Ntusi NB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. Expert Rev Cardiovasc Ther 2009;7:169e80.
16. Damasceno A, Cotter G, Dzudie A, Sliwa K, Mayosi BM. Heart failure in sub-Saharan Africa: time for action. J Am Coll Cardiol 2007;50:1688e93.
17. Dzudie A, Kengne AP, Mbahe S, Menanga A, Kenfack M, Kingue S. Chronic heart failure, selected risk factors and co-morbidities among adults treated for hypertension in a cardiac referral hospital in Cameroon. Eur J Heart Fail 2008;10:367e72.
18. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008;371:915e22.
19. Cygankiewicz I, Zareba W, Vazquez R, Vallverdu M, Gonzalez-Juanatey JR, Valdes M, et al. Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients. Heart Rhythm 2008;5:1095e102.
20. Abdel-Qadir HM, Tu JV, Austin PC, Wang JT, Lee DS. Bundle branch block patterns and long-term outcomes in heart failure. Int J Cardiol 2011;146:213e8.
21. Tabrizi F, Englund A, Rosenqvist M, Wallentin L, Stenestrand U. Influence of left bundle branch block on long-term mortality in a population with heart failure. Eur Heart J 2007;28:2449e55.
22. Hebert K, Quevedo HC, Tamariz L, Dias A, Steen DL, Colombo RA, et al. Prevalence of conduction abnormalities in a systolic heart failure population by race, ethnicity, and gender. Ann Noninvasive Electrocardiol 2012;17:113e22.
23. Hummel SL, Skorcz S, Koelling TM. Prolonged electrocardiogram QRS duration independently predicts long-term mortality in patients hospitalized for heart failure with preserved systolic function. J Card Fail 2009;15:553e60.
24. Wang NC, Maggioni AP, Konstam MA, Zannad F, Krasa HB, Burnett JC Jr, et al. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. JAMA 2008;299:2656e66.
25. Kolo PM, Opadijo OG, Omotoso AB, Balogun MO, Araoye MA, Katibi IA. Prevalence of QTc prolongation in adult Nigerians with chronic heart failure. West Afr J Med 2008;27:69e73.
26. Hawkins NM, Wang D, McMurray JJ, Pfeffer MA, Swedberg K, Granger CB, et al. Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM programme. Heart 2007;93:59e64.
27. Mayosi BM, Keavney B, Kardos A, Davies CH, Ratcliffe PJ, Farrall M, et al. Electrocardiographic measures of left ventricular hypertrophy show greater heritability than echocardiographic left ventricular mass. Eur Heart J 2002;23:1963e71.

Chapter 8. Conclusions and ways forward

Pulmonary hypertension (PH) has progressively moved from an orphan disease to a major public health problem as attested by data from registries in high income countries. However, the condition has yet to be fully characterized around the world. Comparative data on the prevalence of different groups of PH is lacking. Due to the high prevalence of predisposing conditions to PH in sub-Saharan Africa (SSA), knowledge of the profile of patients and distribution of PH aetiologies in this part of the world is a public health priority.

A well designed and managed clinical registry has several advantages. Firstly, it can provide reliable data about cohorts of patients who are likely to be a subset of a larger population with similar disease patterns. Secondly, it provides an opportunity for physicians and scientists at large to generate knowledge about the current epidemiology, actual course and therapies of diseases in the context of their local health system. This information is crucial for an objective estimation of the future health care needs and expenditures. Thirdly, a clinical registry is a basis of hypothesis formulation for further investigation by clinical trials. For all these reasons, a clinical registry of PH across Africa was urgently needed.

In this doctoral research endeavour, using two prospective clinical registries, we have attempted to address several gaps in the knowledge about PH. In the paragraphs below, we summarize our main findings from investigation of specific questions and we suggest main future research directions.

8.1. The clinical profile and distribution of etiologies of pulmonary hypertension in Sub-Saharan Africa.

The analysis of data from the PAPUCO registry, the first multicentric and multinational cohort study of PH in Africa demonstrated that all groups of PH are represented in SSA, with left heart disease (LHD) being the leading cause of PH, followed by HIV and post-tuberculosis lung

disease. PH tend to affect predominantly poorly or uneducated women who are disproportionately exposed to indoor fume, and present late to the hospital. PH-LHD in SSA affects people in their young and active age, and is predominantly due to a number of causes such as heart failure and its different aetiologies, and rheumatic valvular heart disease. Our experience from the PAPUCO registry highlights the potential of generating accurate and reliable data on PH and its aetiologies in SSA. Our findings are likely applicable to other low-income countries at large, and such data are needed to assist health care and policies planning in the region.

Future directions in terms of research on the epidemiology of PH in SSA should include the study of a large sample of PH sub-groups that are almost specific to the LIC including rheumatic valvular heart disease, sickle cell disease and HIV/AIDS. This will help filling the following knowledge gaps:

i. **Rheumatic valvular heart disease:** the updated guidelines by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (1) suggest PH as an indication for surgery in asymptomatic people with mitral regurgitation (MR) if the systolic pulmonary pressure exceeds 50 mmHg at rest or 60 mmHg at effort. However, these guidelines are based on studies in patients with degenerative MR and do not provide enough support for PH in patients with multivalvular lesions as it is usually the case for rheumatic valvular heart disease (150). A study with a large number of patients with rheumatic heart valve disease will facilitate the refinement of knowledge on the added value, if any, of PH to outcome risk stratification in this specific population, and will also improve the understanding of the mechanisms underlying the risk of developing PH. Indeed, there is still very vague understanding of who among patients with valve disease is likely to develop PH, and why in a proportion of these patients with PH due to valve disease, the post capillary and reversible PH will be superimposed by a pre capillary pulmonary vasoconstriction and vascular remodelling leading in some cases to persistent PH event after corrective surgery (86, 187). Also, little information is available on the predictors of persistent PH as well as on the indications for PH specific therapies following corrective surgery for VHD. The pathogenesis of rheumatic heart disease is not fully understood, but suggested to

involve molecular mimicry and genetic predisposition that lead to autoimmune reactions. It would be interesting to investigate whether a subset of this population, due to their genetic background is more likely to develop post capillary PH and subsequent evolution to a pre-capillary component that deserves special attention.

ii. **Sickle cell disease (SCD):** SCD is the most common monogenic disease in humans and a global public health issue, affecting up to 300,000 new-borns each year, with more than 70% of them found in Sub Saharan Africa. As discussed in Chapter one of this thesis, 30% of SCD patients develop PH with increase mortality risk. Current guidelines (32) suggest that these patients should be screened using echocardiogram yearly and undergo right heart catheterization (RHC) if tricuspid velocity by echocardiogram ≥2.5 m/s. A recent study (188) showed that echocardiography alone likely has a low positive predictive value for PH people with SCD, which means the decision on when to either proceed with RHC or further non-invasive monitoring of a patient with SCD remains a clinical challenge. It would be relevant to explore the combined diagnostic utility of all non-invasive tests including ECG, NT-proBNP and echocardiography to correctly identify or exclude PH in SCD patients referred for clinical suspicion of PH. This also applies to the HIV-infected patient's subgroup who have a 2500-fold increased risk of developing PAH.

8.2. The early diagnosis of PH and heart failure in resources-poor settings

Early diagnosis and treatment of PH and its etiological factors is important considering that at the advanced stage, the disease is less amenable to treatment and is associated with poor outcomes. Although RHC is expensive, less available and an invasive test with non-negligible complications, it remains the gold standard for diagnosis of PH. Cost-effective strategies that can assist early diagnosis and distinction between pre and post-capillary PH and therefore avoid unnecessary RHC are warranted. In SSA, 12-lead electrocardiogram (ECG) represents

the more widely available test, relatively inexpensive, simple to perform, objective and reproducible. We assessed in a large sample of ECGs from the THESUS-HF the predictive utility of ECG abnormalities among Africans with acute HF. This study illustrated that ECG abnormalities are almost universal among Africans with acute HF, but most of the abnormalities are non-specific, although some have prognostic value for mortality risk. In a sub-study of the PAPUCO-registry, we similarly found that a normal ECG is rare in patients with PH, but most of these abnormalities were non-specific and ECG criteria of right ventricular strain were rare and also non-specific among patients with PH. It will be important in the future to investigate whether a combination of non-invasive criteria like the six minute walk test, ECG, and NT-proBNP on top of echocardiography helps rule out false positive case of PH among patients referred with dyspnea and suspicion of PH, while not missing true pre-capillary PH. Further research in this area from low income countries should also be directed towards improving diagnosis of HF or PH by an early identification using innovative technologies. For instance, with the wide availability of smartphones in Africa and the low doctor-to-patient ratio (189), it is timely to explore in a larger sample of patients with PH and assess whether mobile ECG (incorporated in smartphones) can be a viable alternative to traditional ECG (which needs medical training for recording) for detecting patients with PH or predisposing conditions. Secondly, the diagnostic capability of recently available and less expensive hand-held echocardiography versus conventional transthoracic DE used as a gold standard in diagnosis of PH will be a key step towards improvement of diagnostic strategies for PH and predisposing conditions in limited resources' settings. Thirdly, novel biomarkers like NT-proBNP have been well shown to predict adverse outcomes in patients with HF and to also serve as a guide to therapy (176). Exploring if NT-pro BNP assay is a good marker for diagnosis and assessment of severity of RV remodeling and PH is another important critical area where further research is needed.

8.3. The outcomes of PH-LHD in Low income countries

In a systematic review, we found that PH-LHD, the main cause of PH, is almost invariably associated with increased mortality risk in patients with LHD. However, evidence originated essentially from studies in high income countries and above all, the effects of PH on

hospitalization risk have been less investigated. What are the effects of PH-LHD on hospitalizations and mortality in Low Income Countries (LIC)? To examine this question, we investigated the clinical profile and short term outcomes of patients with PH-LHD from the multicentre PAPUCO study. We found that left atrium size and tricuspid annular plan excursion (TAPSE) were predictors of RVSP in this cohort. RVSP (but not TAPSE) predicted short term hospitalization but not mortality. In spite of the short term follow-up, these findings raised two important questions: 1) is the absence of an adverse effect of PH-LHD on mortality in this thesis a result of our younger population with a different etiological profile or would an extended follow-up of a larger sample have revealed different results? 2) Can hospitalization risk be reduced in patients with PH-LHD and how can this be achieved? A longer follow-up of a larger population sample with various causes of PH-LHD will help refine the mortality risk and stratification of the management of these patients. Also, the importance of the right ventricular dysfunction in the context of PH-LHD needs further exploration. In the attempt to target PH to reduce outcomes, as described in Chapter one of this thesis, the lack of evidence based advanced therapy in PH-LHD is of great concern. To date, clinical trials have been characterized by limited sample size, single centre, lack of uniform stratification of patients based on PH and finally, unsatisfactory, if not detrimental, results on the outcome of interest. New trials that specifically address PH in left heart disease patients are warranted. In a thesis conducted at the University of Cape Town, G. J. Maarman (190) demonstrated that treatment with melatonin confers cardioprotection in a rat model of PH. As melatonin is inexpensive, safe and already available in several low income countries, a multicentre randomized control trial to evaluate the efficacy and safety of this drug in patients with PH-LHD is a key future step for SSA settings.

In conclusion, several gaps exist in the knowledge of contemporary PH worldwide and specifically in low income countries where the prevalence and burden of PH is estimated to be high due to prevalent predisposing conditions. This thesis has provided greater insight into clinical profile of PH and its aetiologies, PH-LHD predictors and outcome, the diagnostic utility of ECG in PH and finally its prognostic significance in heart failure. It has also raised future research questions for which relevant agendas are delineated.

References

1. Fang JC, DeMarco T, Givertz MM, Borlaug BA, Lewis GD, Rame JE, et al. World Health Organization Pulmonary Hypertension group 2: pulmonary hypertension due to left heart disease in the adult--a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2012 Sep;31(9):913-33.
2. Elliott CG, Barst RJ, Seeger W, Porres-Aguilar M, Brown LM, Zamanian RT, et al. Worldwide physician education and training in pulmonary hypertension: pulmonary vascular disease: the global perspective. Chest. 2010 Jun;137(6 Suppl):85S-94S.
3. Bossone E, Butera G, Bodini BD, Rubenfire M. The interpretation of the electrocardiogram in patients with pulmonary hypertension: the need for clinical correlation. Ital Heart J. 2003 Dec;4(12):850-4.
4. van Wolferen SA, Grunberg K, Vonk Noordegraaf A. Diagnosis and management of pulmonary hypertension over the past 100 years. Respir Med. 2007 Mar;101(3):389-98.
5. Romberg. Uber sklerose der lungen arterie. Dtsch Arch Klin. 1891;48:197–206.
6. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012 Aug;142(2):448-56.
7. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011 Jan;139(1):128-37.
8. Gurtner HP. Aminorex and pulmonary hypertension. A review. Cor Vasa. 1985;27(2-3):160-71.
9. Richards DW. The contributions of right heart catheterization to physiology and medicine, with some observations on the physiopathology of pulmonary heart disease. American heart journal. 1957 Aug;54(2):161-71.
10. Mocumbi AO, Thienemann F, Sliwa K. A Global Perspective on the Epidemiology of Pulmonary Hypertension. Can J Cardiol. 2015 Apr;31(4):375-81.

11. Runo JR, Loyd JE. Primary pulmonary hypertension. Lancet. 2003 May 3;361(9368):1533-44.
12. Bayliss RI, Etheridge MJ, Hyman AL. Pulmonary hypertension in mitral stenosis. Lancet. 1950 Dec 30;2(6644):889-94.
13. Georgiopoulou VV, Kalogeropoulos AP, Borlaug BA, Gheorghiade M, Butler J. Left ventricular dysfunction with pulmonary hypertension: Part 1: epidemiology, pathophysiology, and definitions. Circ Heart Fail. 2013 Mar;6(2):344-54.
14. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation. 2012 Aug 21;126(8):975-90.
15. Wu CT, Wang ZH, Li ZQ, Wang LF. Effect of spironolactone on cardiac remodeling after acute myocardial infarction. World J Emerg Med. 2013;4(1):48-53.
16. Tueller C, Stricker H, Soccal P, Tamm M, Aubert JD, Maggiorini M, et al. Epidemiology of pulmonary hypertension: new data from the Swiss registry. Swiss medical weekly. 2008 Jun 28;138(25-26):379-84.
17. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D42-50.
18. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. Journal of the American College of Cardiology. 2009 Jun 30;54(1 Suppl):S43-54.
19. Hattori N, Kitagawa M, Kitano E. [Dyspnea, coughs, tachycardia and anorexia (thoracic radiography and ECG): (primary pulmonary hypertension)]. Nihon Rinsho. 1977 Fall;35 Suppl 2:2986-7, 3348-9.
20. Proceedings of the 4th World Symposium on Pulmonary Hypertension, February 2008, Dana Point, California, USA. Journal of the American College of Cardiology. 2009 Jun 30;54(1 Suppl):S1-117.
21. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015 Oct;46(4):903-75.

22. Correale M, Palmiotti GA, Lo Storto MM, Montrone D, Foschino Barbaro MP, Di Biase M, et al. HIV-associated pulmonary arterial hypertension: from bedside to the future. Eur J Clin Invest. 2015 Feb 26.
23. Feijoo MQ, Toro R, Lopez Vazquez de la Torre M, Lennie V, Arce C, Moreno V, et al. Relationship between endothelin-1 levels and pulmonary arterial hypertension in HIV-infected patients. AIDS. 2014 Nov 28;28(18):2693-9.
24. Potoka KP, Gladwin MT. Vasculopathy and pulmonary hypertension in sickle cell disease. Am J Physiol Lung Cell Mol Physiol. 2015 Feb 15;308(4):L314-L24.
25. Papamatheakis DG, Mocumbi AO, Kim NH, Mandel J. Schistosomiasis-associated pulmonary hypertension. Pulm Circ. 2014 Dec;4(4):596-611.
26. Graham BB, Mentink-Kane MM, El-Haddad H, Purnell S, Zhang L, Zaiman A, et al. Schistosomiasis-induced experimental pulmonary hypertension: role of interleukin-13 signaling. Am J Pathol. 2010 Sep;177(3):1549-61.
27. Shoukat S, Gowani SA, Taqui AM, Ul Hassan R, Bhutta ZA, Malik AI, et al. Adherence to the European Society of Cardiology (ESC) guidelines for chronic heart failure--a national survey of the cardiologists in Pakistan. BMC cardiovascular disorders. 2011;11:68.
28. Stewart S, Wilkinson D, Becker A, Askew D, Ntyintyane L, McMurray JJ, et al. Mapping the emergence of heart disease in a black, urban population in Africa: the Heart of Soweto Study. International journal of cardiology. 2006 Mar 22;108(1):101-8.
29. Tibazarwa K, Ntyintyane L, Sliwa K, Gerntholtz T, Carrington M, Wilkinson D, et al. A time bomb of cardiovascular risk factors in South Africa: results from the Heart of Soweto Study "Heart Awareness Days". International journal of cardiology. 2009 Feb 20;132(2):233-9.
30. Stringham R, Shah NR. Pulmonary arterial hypertension: an update on diagnosis and treatment. Am Fam Physician. 2010 Aug 15;82(4):370-7.
31. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. Journal of the American College of Cardiology. 2009 Apr 28;53(17):1573-619.
32. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American

College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009 Apr 28;119(16):2250-94.

33. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. European heart journal. 2001 Sep;22(17):1527-60.
34. The National Institute for Clinical Excellence (August, 2010). Management of chronic heart failure in adults in primary and secondary care. NICE Guideline. Available at http://guidance.nice.org.uk/CG108/Guidance/pdf/English, accessed November 2015.
35. The National Institute for Clinical Excellence. Management of chronic heart failure in adults in primary and secondary care. NICE Guideline Available at wwwniceorguk. 2003;5.
36. Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, et al. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. European journal of heart failure. 2007 May;9(5):491-501.
37. Ambrusko SJ, Gunawardena S, Sakara A, Windsor B, Lanford L, Michelson P, et al. Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. Pediatr Blood Cancer. 2006 Dec;47(7):907-13.
38. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, et al. The prognostic role of the ECG in primary pulmonary hypertension. Chest. 2002 Feb;121(2):513-8.
39. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010 Jul;23(7):685-713; quiz 86-8.
40. Beigel R, Cercek B, Luo H, Siegel RJ. Noninvasive evaluation of right atrial pressure. J Am Soc Echocardiogr. 2013 Sep;26(9):1033-42.
41. Thienemann F, Dzudie A, Mocumbi AO, Blauwet L, Sani MU, Karaye KM, et al. Rationale and design of the Pan African Pulmonary hypertension Cohort (PAPUCO) study: implementing a contemporary registry on pulmonary hypertension in Africa. BMJ open. 2014;4(10):e005950.

42. Furlow B. Pulmonary hypertension of sickle cell disease: new guidelines. Lancet Respir Med. 2014 Apr;2(4):263.
43. Henkens IR, Gan CT, van Wolferen SA, Hew M, Boonstra A, Twisk JW, et al. ECG monitoring of treatment response in pulmonary arterial hypertension patients. Chest. 2008 Dec;134(6):1250-7.
44. Machraoui A, Helfen A, von Dryander S, Schott D, Ulmer WT, Barmeyer J. [Diagnostic value of right thoracic ECG recording in detection of pulmonary hypertension in chronic obstructive respiratory disease]. Herz. 1994 Jun;19(3):182-8.
45. Gurtner HP. [Accumulation of primary vascular pulmonary hypertension in Switzerland during 1967-1970. Introduction]. Schweiz Med Wochenschr. 1970 Dec 12;100(50):2146-7.
46. Gurtner HP. [Pulmonary hypertension following appetite depressants]. Med Welt. 1972 Jul 22;23(29):1036-41.
47. Takatsu T, Tanaka T, Kitaura Y, Kubo S, Hori K. [Primary pulmonary hypertension--classification of pulmonary hypertension]. Nihon Rinsho. 1976;34(3):554-63.
48. Bruner LH, Hilliker KS, Roth RA. Pulmonary hypertension and ECG changes from monocrotaline pyrrole in the rat. The American journal of physiology. 1983 Aug;245(2):H300-6.
49. Jezkova L, Fucik J, Michaljanic A, Krasa H, Jezek V. [ECG and its significance for pulmonary hypertension diagnosis and for the estimation of prognosis in cryptogenic fibrosing pulmonary alveolitis (author's transl)]. Cas Lek Cesk. 1981 Sep 3;120(35):1050-4.
50. Proceedings of the 3rd World Symposium on Pulmonary Arterial Hypertension. Venice, Italy, June 23-25, 2003. Journal of the American College of Cardiology. 2004 Jun 16;43(12 Suppl S):1S-90S.
51. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. Journal of the American College of Cardiology. 2004 Jun 16;43(12 Suppl S):5S-12S.
52. Rosenkranz S, Bonderman D, Buerke M, Felgendreher R, ten Freyhaus H, Grunig E, et al. Pulmonary hypertension due to left heart disease: updated Recommendations of the Cologne Consensus Conference 2011. Int J Cardiol. 2011 Dec;154 Suppl 1:S34-44.

53. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. Journal of the American College of Cardiology. 2013 Dec 24;62(25 Suppl):D34-41.
54. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European heart journal. 2012 Jul;33(14):1787-847.
55. Stephen B, Dalal P, Berger M, Schweitzer P, Hecht S. Noninvasive estimation of pulmonary artery diastolic pressure in patients with tricuspid regurgitation by Doppler echocardiography. Chest. 1999 Jul;116(1):73-7.
56. Humbert M, Montani D, Evgenov OV, Simonneau G. Definition and classification of pulmonary hypertension. Handb Exp Pharmacol. 2013;218:3-29.
57. Heunisch K, Luschnitz E, Butter U, Lobe J. [Correlation of lung perfusion scintigraphy, roentgenologic findings, ECG and lung function tests in lung diseases with pulmonary hypertension]. Z Gesamte Inn Med. 1973 Dec 15;28(24):762-5.
58. Vivo RP, Krim SR, Krim NR, Zhao X, Hernandez AF, Peterson ED, et al. Care and outcomes of Hispanic patients admitted with heart failure with preserved or reduced ejection fraction: findings from get with the guidelines-heart failure. Circ Heart Fail. 2012 Mar 1;5(2):167-75.
59. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. Journal of the American College of Cardiology. 2006 Dec 19;48(12):2546-52.
60. Corra U, Giannuzzi P, Adamopoulos S, Bjornstad H, Bjarnason-Weherns B, Cohen-Solal A, et al. Executive summary of the position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology (ESC): core components of cardiac rehabilitation in chronic heart failure. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2005 Aug;12(4):321-5.

61. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart. 2012 Dec;98(24):1805-11.
62. Bursi F, McNallan SM, Redfield MM, Nkomo VT, Lam CSP, Weston SA, et al. Pulmonary Pressures and Death in Heart FailureA Community Study. Journal of the American College of Cardiology. 2012;59(3):222-31.
63. Abramson SV, Burke JF, Kelly JJ, Jr., Kitchen JG, 3rd, Dougherty MJ, Yih DF, et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Annals of internal medicine. 1992 Jun 1;116(11):888-95.
64. Szwejkowski BR, Elder DH, Shearer F, Jack D, Choy AM, Pringle SD, et al. Pulmonary hypertension predicts all-cause mortality in patients with heart failure: a retrospective cohort study. European journal of heart failure. 2012 Feb;14(2):162-7.
65. Carrasco-Sanchez FJ, Ortiz-Lopez E, Galisteo-Almeda L, Camacho-Vazquez C, Ruiz-Frutos C, Pujol-De La Llave E. [Prognostic importance of pulmonary hypertension in heart failure with preserved ejection fraction]. Rev Clin Esp. 2010 Nov;210(10):489-96.
66. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. Journal of the American College of Cardiology. 2009 Mar 31;53(13):1119-26.
67. Damy T, Goode KM, Kallvikbacka-Bennett A, Lewinter C, Hobkirk J, Nikitin NP, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. European heart journal. 2010 Sep;31(18):2280-90.
68. Leung CC, Moondra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. The American journal of cardiology. 2010 Jul 15;106(2):284-6.
69. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. American journal of respiratory and critical care medicine. 2006 May 1;173(9):1023-30.
70. Makubi A, Hage C, Lwakatare J, Mmbando B, Kisenge P, Lund LH, et al. Prevalence and prognostic implications of anaemia and iron deficiency in Tanzanian patients with heart failure. Heart. 2015 Apr;101(8):592-9.

71. Torres-Macho J, Delgado-Jimenez JF, Sanz-Salvo J, Gonzalez-Mansilla A, Sanchez-Sanchez V, Gamez-Diez S, et al. Predictors of pulmonary hypertension in patients with end-stage heart failure. Congest Heart Fail. 2012 Jul-Aug;18(4):212-6.
72. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. Journal of the American College of Cardiology. 1999 Nov 15;34(6):1802-6.
73. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. Journal of the American College of Cardiology. 2001;37(1):183-8.
74. Cappola TP, Felker GM, Kao WH, Hare JM, Baughman KL, Kasper EK. Pulmonary hypertension and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. Circulation. 2002 Apr 9;105(14):1663-8.
75. Grigioni F, Potena L, Galie N, Fallani F, Bigliardi M, Coccolo F, et al. Prognostic implications of serial assessments of pulmonary hypertension in severe chronic heart failure. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2006 Oct;25(10):1241-6.
76. Shalaby A, Voigt A, El-Saed A, Saba S. Usefulness of Pulmonary Artery Pressure by Echocardiography to Predict Outcome in Patients Receiving Cardiac Resynchronization Therapy Heart Failure. The American Journal of Cardiology. 2008;101(2):238-41.
77. Adhyapak SM. Effect of right ventricular function and pulmonary pressures on heart failure prognosis. Preventive cardiology. 2010;13(2):72-7.
78. Miller WL, Mahoney DW, Michelena HI, Pislaru SV, Topilsky Y, Enriquez-Sarano M. Contribution of ventricular diastolic dysfunction to pulmonary hypertension complicating chronic systolic heart failure. JACC Cardiovasc Imaging. 2011 Sep;4(9):946-54.
79. Karaye KM, Saidu H, Bala MS, Yahaya IA. Prevalence, clinical characteristics and outcome of pulmonary hypertension among admitted heart failure patients. Ann Afr Med. 2013 Oct-Dec;12(4):197-204.
80. Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Kober L, Torp-Pedersen C, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. The American journal of cardiology. 2007 Apr 15;99(8):1146-50.

81. Khush KK, Tasissa G, Butler J, McGlothlin D, De Marco T. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: Analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. American Heart Journal. 2009;157(6):1026-34.
82. Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. Circ Heart Fail. 2011 Sep;4(5):644-50.
83. Lam CSP, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Community-Based Study. Journal of the American College of Cardiology. 2009;53(13):1119-26.
84. Tatebe S, Fukumoto Y, Sugimura K, Miyamichi-Yamamoto S, Aoki T, Miura Y, et al. Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease. Circ J. 2012;76(5):1235-44.
85. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation. 2001 Dec 4;104(23):2797-802.
86. Haddad F, Kudelko K, Mercier O, Vrtovec B, Zamanian RT, de Jesus Perez V. Pulmonary hypertension associated with left heart disease: characteristics, emerging concepts, and treatment strategies. Progress in cardiovascular diseases. 2011 Sep-Oct;54(2):154-67.
87. Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives. Circ Heart Fail. 2014 Mar 1;7(2):367-77.
88. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. [Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)]. G Ital Cardiol (Rome). 2013 Mar;14(3):167-214.
89. Fawzy ME, Hassan W, Stefadouros M, Moursi M, El Shaer F, Chaudhary MA. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotomy. J Heart Valve Dis. 2004 Nov;13(6):942-7; discussion 7-8.

90. Hart SA, Krasuski RA, Wang A, Kisslo K, Harrison JK, Bashore TM. Pulmonary hypertension and elevated transpulmonary gradient in patients with mitral stenosis. J Heart Valve Dis. 2010 Nov;19(6):708-15.
91. Ghoreishi M, Evans CF, DeFilippi CR, Hobbs G, Young CA, Griffith BP, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. J Thorac Cardiovasc Surg. 2011 Dec;142(6):1439-52.
92. Barbieri A, Bursi F, Grigioni F, Tribouilloy C, Avierinos JF, Michelena HI, et al. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. European heart journal. 2011 Mar;32(6):751-9.
93. Magne J, Lancellotti P, Pierard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. Circulation. 2010 Jul 6;122(1):33-41.
94. Silver K, Aurigemma G, Krendel S, Barry N, Ockene I, Alpert J. Pulmonary artery hypertension in severe aortic stenosis: incidence and mechanism. American heart journal. 1993 Jan;125(1):146-50.
95. Khandhar S, Varadarajan P, Turk R, Sampat U, Patel R, Kamath A, et al. Survival benefit of aortic valve replacement in patients with severe aortic regurgitation and pulmonary hypertension. Ann Thorac Surg. 2009 Sep;88(3):752-6.
96. Ward C, Hancock BW. Extreme pulmonary hypertension caused by mitral valve disease. Natural history and results of surgery. British heart journal. 1975 Jan;37(1):74-8.
97. Nozohoor S, Hyllen S, Meurling C, Wierup P, Sjogren J. Prognostic value of pulmonary hypertension in patients undergoing surgery for degenerative mitral valve disease with leaflet prolapse. Journal of cardiac surgery. 2012 Nov;27(6):668-75.
98. Johnson LW, Hapanowicz MB, Buonanno C, Bowser MA, Marvasti MA, Parker FB, Jr. Pulmonary hypertension in isolated aortic stenosis. Hemodynamic correlations and follow-up. J Thorac Cardiovasc Surg. 1988 Apr;95(4):603-7.
99. Ben-Dor I, Goldstein SA, Pichard AD, Satler LF, Maluenda G, Li Y, et al. Clinical profile, prognostic implication, and response to treatment of pulmonary hypertension in patients with severe aortic stenosis. The American journal of cardiology. 2011 Apr 1;107(7):1046-51.

100. Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano RJ, Jr. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. J Thorac Cardiovasc Surg. 2011 Jun;141(6):1424-30.

101. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011 Jul 12;124(2):164-74.

102. Luscher TF, Enseleit F, Pacher R, Mitrovic V, Schulze MR, Willenbrock R, et al. Hemodynamic and neurohumoral effects of selective endothelin A (ET(A)) receptor blockade in chronic heart failure: the Heart Failure ET(A) Receptor Blockade Trial (HEAT). Circulation. 2002 Nov 19;106(21):2666-72.

103. Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? International journal of cardiology. 2002 Oct;85(2-3):195-7.

104. Anand I, McMurray J, Cohn JN, Konstam MA, Notter T, Quitzau K, et al. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. Lancet. 2004 Jul 24-30;364(9431):347-54.

105. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA : the journal of the American Medical Association. 2013 Mar 27;309(12):1268-77.

106. Bonderman D, Ghio S, Felix SB, Ghofrani HA, Michelakis E, Mitrovic V, et al. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. Circulation. 2013 Jul 30;128(5):502-11.

107. Packer M, McMurray J, Massie BM, Caspi A, Charlon V, Cohen-Solal A, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail. 2005 Feb;11(1):12-20.

108. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure:

The Flolan International Randomized Survival Trial (FIRST). American Heart Journal. 1997 Jul;134(1):44-54.

109. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension due to left heart diseases. Journal of the American College of Cardiology. 2013 Dec 24;62(25 Suppl):D100-8.

110. Stewart S, Mocumbi AO, Carrington MJ, Pretorius S, Burton R, Sliwa K. A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. European journal of heart failure. 2011 Oct;13(10):1070-7.

111. Mocumbi AO, Lameira E, Yaksh A, Paul L, Ferreira MB, Sidi D. Challenges on the management of congenital heart disease in developing countries. Int J Cardiol. 2011 May 5;148(3):285-8.

112. Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. Clin Res Cardiol. 2010 Feb;99(2):65-74.

113. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. Arch Intern Med. 2012 Oct 8;172(18):1386-94.

114. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. International journal of cardiology. 2014 Feb 15;171(3):368-76.

115. Ntusi NB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. Expert review of cardiovascular therapy. 2009 Feb;7(2):169-80.

116. Damasceno A, Cotter G, Dzudie A, Sliwa K, Mayosi BM. Heart failure in sub-saharan Africa: time for action. J Am Coll Cardiol. 2007 Oct 23;50(17):1688-93.

117. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. European heart journal. 2008 Jan;29(2):270-6.

118. Dahoui HA, Hayek MN, Nietert PJ, Arabi MT, Muwakkit SA, Saab RH, et al. Pulmonary hypertension in children and young adults with sickle cell disease: evidence for familial clustering. Pediatr Blood Cancer. 2010 Mar;54(3):398-402.

119. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med. 2011 Jul 7;365(1):44-53.

120. McGoon MD, Krichman A, Farber HW, Barst RJ, Raskob GE, Liou TG, et al. Design of the REVEAL registry for US patients with pulmonary arterial hypertension. Mayo Clinic proceedings. 2008 Aug;83(8):923-31.

121. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA : the journal of the American Medical Association. 2013 Nov 27;310(20):2191-4.

122. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA : the journal of the American Medical Association. 1997 Mar 19;277(11):925-6.

123. The Pan African Pulmonary Hypertension Cohort Registry; Description. Retrieved from:https://clinicaltrials.gov/ct2/show/NCT02265887, Last Accessed: 04/7/15.

124. "Key to HDI countries and ranks, 2013". Human Development Report United Nations Development Programme. p. 159. Retrieved 26 July 2014.

125. http://hdr.undp.org/sites/default/files/Country-Profiles/CMR.pdf. Accessed march 2015.

126. http://www.statistics-cameroon.org/downloads/annuaire2010/chap4.pdf. Accessed march 2015.

127. Humbert M. The burden of pulmonary hypertension. Eur Respir J. 2007 Jul;30(1):1-2.

128. Ristow B, Schiller NB. Pulmonary hypertension in sickle cell disease. N Engl J Med. 2011 Oct 27;365(17):1645-6; author reply 8-9.

129. Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004 Jul;126(1 Suppl):7S-10S.

130. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. Circulation. 1980 Aug;62(2):212-7.

131. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989 Sep-Oct;2(5):358-67.

132. Schiller NB. Two-dimensional echocardiographic determination of left ventricular volume, systolic function, and mass. Summary and discussion of the 1989

recommendations of the American Society of Echocardiography. Circulation. 1991 Sep;84(3 Suppl):I280-7.

133. Ghio S, Temporelli PL, Klersy C, Simioniuc A, Girardi B, Scelsi L, et al. Prognostic relevance of a non-invasive evaluation of right ventricular function and pulmonary artery pressure in patients with chronic heart failure. European Journal of Heart Failure. 2013 April 1, 2013;15(4):408-14.

134. Lanzarini L, Fontana A, Lucca E, Campana C, Klersy C. Noninvasive estimation of both systolic and diastolic pulmonary artery pressure from Doppler analysis of tricuspid regurgitant velocity spectrum in patients with chronic heart failure. American heart journal. 2002 Dec;144(6):1087-94.

135. Temporelli PL, Scapellato F, Eleuteri E, Imparato A, Giannuzzi P. Doppler echocardiography in advanced systolic heart failure: a noninvasive alternative to Swan-Ganz catheter. Circ Heart Fail. 2010 May;3(3):387-94.

136. Oh JK, Pellikka PA, Panza JA, Biernat J, Attisano T, Manahan BG, et al. Core lab analysis of baseline echocardiographic studies in the STICH trial and recommendation for use of echocardiography in future clinical trials. J Am Soc Echocardiogr. 2012 Mar;25(3):327-36.

137. Mansencal N, d'Allonnes LR, Beauchet A, Fabre S, Digne F, Farcot JC, et al. Reliability of echocardiography for hemodynamic assessment of end-stage heart failure. The American journal of cardiology. 2007 Sep 15;100(6):998-1001.

138. Nagueh SF, Bhatt R, Vivo RP, Krim SR, Sarvari SI, Russell K, et al. Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. Circulation Cardiovascular imaging. 2011 May;4(3):220-7.

139. McClanahan A, Guglin M. Right ventricular dysfunction compromises accuracy of echocardiographic diagnosis of pulmonary hypertension in heart failure. J Card Fail. 2011 Dec;17(12):1023-7.

140. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA : the journal of the American Medical Association. 2005 Oct 5;294(13):1625-33.

141. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of

Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). European heart journal. 2009 Oct;30(20):2493-537.

142. Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. BMC medical research methodology. 2012;12:96.

143. Gidwani S, Nair A. The burden of pulmonary hypertension in resource-limited settings. Global heart. 2014 Sep;9(3):297-310.

144. Global status of immunization safety: a report based on the WHO/UNICEF joint reporting form. Wkly Epidemiol Rec. 2003 Feb 14;78(7):42-7.

145. Msamanga GI, Fawzi WW. The double burden of HIV infection and tuberculosis in sub-Saharan Africa. The New England journal of medicine. 1997 Sep 18;337(12):849-51.

146. McGoon MD, Benza RL, Escribano-Subias P, Jiang X, Miller DP, Peacock AJ, et al. Pulmonary arterial hypertension: epidemiology and registries. Journal of the American College of Cardiology. 2013 Dec 24;62(25 Suppl):D51-9.

147. Pittrow D, Ghofrani HA, Opitz CF, Huscher D, Hoeper MM. [International, prospective register for the documentation of first-line and maintenance therapy in patients with pulmonary hypertension (CompERA-XL)]. Dtsch Med Wochenschr. 2009 Aug;134 Suppl 5:S173-5.

148. COMPERA; Estimated Study Completion Date: May 2016. Retrieved from:https://clinicaltrials.gov/ct2/show/NCT01347216, Last Accessed: 04/7/15.

149. Enea I, Ghio S, Bongarzoni A, Casazza F, D'Armini AM, Favretto G, et al. [Echocardiographic alterations suggestive of pulmonary hypertension in the Italian ultrasonography laboratories. Epidemiological data from the INCIPIT study (INCidence of Pulmonary Hypertension in Italian ulTrasonography laboratories)]. G Ital Cardiol (Rome). 2010 May;11(5):402-7.

150. Zuhlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). European heart journal. 2015 May 7;36(18):1115-22.

151. Stricker H, Domenighetti G, Popov W, Speich R, Nicod L, Aubert JD, et al. Severe pulmonary hypertension: data from the Swiss Registry. Swiss medical weekly. 2001 Jun 16;131(23-24):346-50.

152. Manes A, Palazzini M, Dardi F, D'Adamo A, Rinaldi A, Galie N. [Female gender and pulmonary arterial hypertension: a complex relationship]. G Ital Cardiol (Rome). 2012 Jun;13(6):448-60.

153. Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. Pulm Circ. 2013 Jan;3(1):89-94.

154. Hoette S, Jardim C, Souza R. Diagnosis and treatment of pulmonary hypertension: an update. J Bras Pneumol. 2010 Nov-Dec;36(6):795-811.

155. Jacobson B. Anticoagulation in South Africa--a dangerous necessity. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2006 Aug;96(8):694.

156. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. Journal of the American College of Cardiology. 2001 Apr;37(5):1228-33.

157. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010 Jul 13;122(2):164-72.

158. Benza RL. Pulmonary hypertension associated with sickle cell disease: pathophysiology and rationale for treatment. Lung. 2008 Jul-Aug;186(4):247-54.

159. Ogah OS, Sliwa K, Akinyemi JO, Falase AO, Stewart S. Hypertensive heart failure in Nigerian Africans: insights from the Abeokuta Heart Failure Registry. Journal of clinical hypertension. 2015 Apr;17(4):263-72.

160. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan;28(1):1-39 e14.

161. Merlos P, Nunez J, Sanchis J, Minana G, Palau P, Bodi V, et al. Echocardiographic estimation of pulmonary arterial systolic pressure in acute heart failure. Prognostic implications. European journal of internal medicine. 2013;24(6):562-7.

162. Zuern CS, Eick C, Rizas K, Stoleriu C, Woernle B, Wildhirt S, et al. Prognostic value of mild-to-moderate pulmonary hypertension in patients with severe aortic valve stenosis undergoing aortic valve replacement. Clin Res Cardiol. 2012 Feb;101(2):81-8.

163. Margetts B. Feedback on WHO/FAO global report on diet, nutrition and prevention of chronic diseases(NCD). Public Health Nutr. 2003 Aug;6(5):423-4; discussion 5, 7-9.

164. Enriquez-Sarano M, Rossi A, Seward JB, Bailey KR, Tajik AJ. Determinants of pulmonary hypertension in left ventricular dysfunction. Journal of the American College of Cardiology. 1997 Jan;29(1):153-9.

165. Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, et al. Contemporary profile of acute heart failure in Southern Nigeria: data from the Abeokuta Heart Failure Clinical Registry. JACC Heart Fail. 2014 Jun;2(3):250-9.

166. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. Circulation. 2009 May 26;119(20):2663-70.

167. Gan CT, McCann GP, Marcus JT, van Wolferen SA, Twisk JW, Boonstra A, et al. NT-proBNP reflects right ventricular structure and function in pulmonary hypertension. Eur Respir J. 2006 Dec;28(6):1190-4.

168. Mutlak D, Aronson D, Carasso S, Lessick J, Reisner SA, Agmon Y. Frequency, determinants and outcome of pulmonary hypertension in patients with aortic valve stenosis. Am J Med Sci. 2012 May;343(5):397-401.

169. Ristow B, Ali S, Ren X, Whooley MA, Schiller NB. Elevated pulmonary artery pressure by Doppler echocardiography predicts hospitalization for heart failure and mortality in ambulatory stable coronary artery disease: the Heart and Soul Study. Journal of the American College of Cardiology. 2007 Jan 2;49(1):43-9.

170. Maschmeyer G, Haas A, Dickerhoff R, Kleber FX. [Pulmonary hypertension in sickle cell disease--epidemiology, pathogenesis, diagnosis and treatment]. Dtsch Med Wochenschr. 2007 Jan 19;132(3):103-7.

171. Lau KC, Frank DB, Hanna BD, Patel AR. Utility of electrocardiogram in the assessment and monitoring of pulmonary hypertension (idiopathic or secondary to pulmonary

developmental abnormalities) in patients</=18 years of age. The American journal of cardiology. 2014 Jul 15;114(2):294-9.

172. Kato GJ, Hsieh M, Machado R, Taylor Jt, Little J, Butman JA, et al. Cerebrovascular disease associated with sickle cell pulmonary hypertension. Am J Hematol. 2006 Jul;81(7):503-10.

173. Goncalvesova E, Luknar M, Lesny P. ECG signs of right ventricular hypertrophy may help distinguish pulmonary arterial hypertension and pulmonary hypertension due to left ventricular diastolic dysfunction. Bratislavske lekarske listy. 2011;112(11):614-8.

174. Kato GJ, McGowan V, Machado RF, Little JA, Taylor Jt, Morris CR, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood. 2006 Mar 15;107(6):2279-85.

175. Sliwa K, Lee GA, Carrington MJ, Obel P, Okreglicki A, Stewart S. Redefining the ECG in urban South Africans: electrocardiographic findings in heart disease-free Africans. International journal of cardiology. 2013 Sep 1;167(5):2204-9.

176. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. Journal of the American College of Cardiology. 2007 Apr 24;49(16):1733-9.

177. Dzudie A, Milo O, Edwards C, Cotter G, Davison BA, Damasceno A, et al. Prognostic Significance of ECG Abnormalities for Mortality Risk in Acute Heart Failure: Insight From the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF). J Card Fail. 2014 Jan;20(1):45-52.

178. Karaye KM, Sani MU. Electrocardiographic abnormalities in patients with heart failure. Cardiovasc J Afr. 2008 Jan-Feb;19(1):22-5.

179. Varma N. Role of the surface electrocardiogram in developing countries. J Electrocardiol. 2010 Nov-Dec;43(6):612-4.

180. Al-Naamani K, Hijal T, Nguyen V, Andrew S, Nguyen T, Huynh T. Predictive values of the electrocardiogram in diagnosing pulmonary hypertension. International journal of cardiology. 2008 Jul 4;127(2):214-8.

181. Kopec G, Tyrka A, Miszalski-Jamka T, Sobien M, Waligora M, Brozda M, et al. Electrocardiogram for the diagnosis of right ventricular hypertrophy and dilation in idiopathic pulmonary arterial hypertension. Circ J. 2012;76(7):1744-9.

182. Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, et al. Short-term outcomes after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria: data from the Abeokuta Heart Failure Registry. Cardiovasc J Afr. 2014 Sep-Oct;25(5):217-23.

183. Castro O, Gladwin MT. Pulmonary hypertension in sickle cell disease: mechanisms, diagnosis, and management. Hematol Oncol Clin North Am. 2005 Oct;19(5):881-96, vii.

184. Bonderman D, Wexberg P, Heinzl H, Lang IM. Non-invasive algorithms for the diagnosis of pulmonary hypertension. Thrombosis and haemostasis. 2012 Dec;108(6):1037-41.

185. McKelvie RS, Moe GW, Ezekowitz JA, Heckman GA, Costigan J, Ducharme A, et al. The 2012 Canadian Cardiovascular Society heart failure management guidelines update: focus on acute and chronic heart failure. Can J Cardiol. 2013 Feb;29(2):168-81.

186. Cotter G, Cotter-Davison B, Ogah OS. The burden of heart failure in Africa. European journal of heart failure. 2013 Aug;15(8):829-31.

187. Cheli M, Vachiery JL. Controversies in pulmonary hypertension due to left heart disease. F1000Prime Rep. 2015;7:07.

188. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. The New England journal of medicine. 2011 Jul 7;365(1):44-53.

189. Dalton SC. The current crisis in human resources for health in Africa: the time to adjust our focus is now. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2014 Sep;108(9):526-7.

190. Maarman. GJ. (2014). Melatonin as a novel cardioprotective therapy in Pulmonary Hypertension. (Doctoral thesis, University of Cape Town, South Africa). Retrieved from https://open.uct.ac.za/bitstream/.../thesis_hsf_2014_maarman_gj.pdf

Appendices

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THESUS-HF : CASE REPORT FORM

Baseline

Patient Number: __ __ – __ __ __ Patient's Initials: __ __ __

Demographics

1 Date of admission: __ __ / __ __ __ /200 __ (day / month / year) Time: __ __ : __ __ (00:00 to 23:59)

2 Date of birth: __ __ / __ __ __ / __ __ __ __ (day / month / year)

3 Sex: 1 Male 1 Female

4 Race: 1 Black 2 Asian 3 Caucasian

5 Height: ___ ___ ___ cm

6 Weight: ___ ___ ___ kg

Pre-Admission

1 Number of acute heart failure *(AHF)* admissions in the last 12 months: ___ ___

2 Date of last acute heart failure *(AHF)* admission: __ __ / __ __ __ /200 __ (day / month / year) OR 96 NA

3 NYHA *(New York Heart Association)* classification 1 month prior to admission: I II III IV NA

ECG (Electrocardiogram)

Please attach copy of admission ECG in the CRF divider pocket.

Baseline Labs First obtained at Admission

	Lab	Value	Units
1	Creatinine	_____	mg/dL µmol/L
2	BUN *(blood urea nitrogen)*/urea	_____	mg/dL mmol/L
3	Sodium	_____	mmol/L mEq/L
4	Glucose	_____	mg/dL mmol/L
5	Hemoglobin	_____	g/L mmol/L g/dL
6	Total WBC *(white blood count)*	_____	x10 9/L or 10 3/mm3 /mm3 or /cumm or /µL or /mcL
7	Lymphocytes %	_____	%
8	Cholesterol	_____	mg/dL mmol/L
9	Triglycerides	_____	mg/dL mmol/L
10	Peak CK *(creatine kinase)*	_____	IU/L µkat/L nkat/L
11	Peak CK-MB *(creatinine kinase myocardial band)*	_____	IU/L µg/L µkat/L ng/mL nkat/L %
12	Peak Troponin	_____	ng/mL
13	NT Pro BNP *(N Terminal Prohormone B-type natriuretic peptide)*	_____	pg/mL OR BNP _____ pg/mL

THESUS-HF

Baseline

Patient Number: __ __ – __ __ __ Patient's Initials: __ __ __

Baseline Characteristics at Time of Admission

1 Diabetes ..... 0 No 1 Yes → If Yes: Check all that apply: Diet Oral Insulin

2 Ischemic heart disease ..... 0 No 1 Yes → If Yes: Check all that apply:

History of MI *(myocardial infarction)*
History of CABG *(coronary artery bypass graft)*
History of PCI *(percutaneous coronary intervention)*
Stable angina → If Yes: Canadian Cardiovascular Society Class. of angina: I II III IV

3 Valvular disease ..... 0 No 1 Yes → If Yes: Check all that apply:

Mitral stenosis
Mitral regurgitation
Aortic stenosis
Aortic regurgitation
Other *(specify)*: _____

4 HIV test positive 99 Unknown 0 No 1 Yes → If Yes: Antiretroviral therapy? 0 No 1 Yes

5 Hypertension ..... 0 No 1 Yes

6 Hyperlipidemia ..... 0 No 1 Yes

7 Stroke ..... 0 No 1 Yes

8 PVD *(peripheral vascular disease)* .... 0 No 1 Yes

9 Smoking ..... 0 No 1 Yes

10 Malignancy ..... 0 No 1 Yes

11 Depression ..... 0 No 1 Yes

12 Dementia ..... 0 No 1 Yes

13 Atrial fibrillation ..... 0 No 1 Yes

14 Pacemaker ..... 0 No 1 Yes

15 Pericardial disease ..... 0 No 1 Yes

16 Cardiomyopathy ..... 0 No 1 Yes

17 Cor pulmonale ..... 0 No 1 Yes

18 Ejection fraction: _____ %

THESUS-HF

Hospitalization

Patient Number: __ __ – __ __ __ Patient's Initials: __ __ __

Hospital Data See opposite page for instructions

Date →		___/_____/200__ day month year	__/_____/200__ day month year	__/_____/200__ day month year	__/_____/200__ day month year	__/_____/200__ day month year	__/_____/200__ day month year
1 Symptom	**Scale**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
Dyspnea	+3 to –3	NA	NA	_____	_____	_____	_____
Well-being	+3 to –3	NA	NA	_____	_____	_____	_____
Orthopnea	0 to 3	_____	_____	_____	_____	_____	_____
Dyspnea on exertion	0 to 3 OR NA *(not evaluable)*	_____ NA	_____ NA	_____ NA	_____ NA	_____ NA	_____ NA
2 Signs	**Scale**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
Blood pressure	systolic/diastolic	__ __ __/__ __ __	__ __ __/__ __ __	__ __ __/__ __ __	__ __ __/__ __ __	__ __ __/__ __ __	__ __ __/__ __ __
Heart rate	beats/minute	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
Respiration	breaths/minute	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
O_2 saturation	%	___ ___.___	___ ___.___	___ ___.___	___ ___.___	___ ___.___	___ ___.___
Temperature	°C	___ ___.___	___ ___.___	___ ___.___	___ ___.___	___ ___.___	___ ___.___
Peripheral edema	0 to 3+	_____	_____	_____	_____	_____	_____
Rales	0 to 3	_____	_____	_____	_____	_____	_____
JVP *(Jugular venous pressure)*	1 to 3 OR NA *(not evaluable)*	_____ NA	_____ NA	_____ NA	_____ NA	_____ NA	_____ NA
Weight	kg	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
3 Labs	**Unit**	**1 Month Pre**	**Admission***	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
Creatinine	mg/dL µmol/L	_____	NA*	_____	_____	_____	_____
BUN/urea	mg/dL mmol/L	_____	NA*	_____	_____	_____	_____
Sodium	mmol/L mEq/L	_____	NA*	_____	_____	_____	_____
BNP	pg/mL	_____	NA*	_____	_____	_____	_____
NT Pro BNP	pg/mL	_____	NA*	_____	_____	_____	_____

*Record admission lab values on CRF page 1.

THESUS-HF

Hospitalization

Patient Number: ___ ___ – ___ ___ ___ Patient's Initials: ___ ___ ___

Hospital Data See opposite page for instructions (continued)

4 IV Drugs	1 Month Pre	Admission	Day 1	Day 2	Discharge or Day 7	Follow Up
Nitrates	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Furosemide	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Dopamine	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Dobutamine	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Digoxin	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Mechanical ventilation	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
5 PO Drugs	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
ACE inhibitors/ angiotensin antagonists	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Loop diuretics	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Beta blockers	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Digoxin	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Hydralazine	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Nitrates	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Aldosterone inhibitor	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Statins	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Aspirin	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Anticoagulants	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes

Outcomes

Patient Number: __ __ – __ __ __ Patient's Initials: __ __ __

Outcome

Hospital discharge date: __ __ / __ __ __ / 200 __
(day / month / year)

Rehospitalization Within 6 Months

	Rehospitalization #1	Rehospitalization #2	Rehospitalization #3
Admission Date →	__ __ / __ __ __ / 200 __ (day / month / year)	__ __ / __ __ __ / 200 __ (day / month / year)	__ __ / __ __ __ / 200 __ (day / month / year)
Reason for Rehospitalization			
Heart Failure	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Ischemia	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Arrhythmia	0 No 1 Yes	0 No 1 Yes	0 No 1 Yes
Other cardiac	0 No 1 Yes → Specify: _____	0 No 1 Yes → Specify: _____	0 No 1 Yes → Specify: _____
Non-cardiac	0 No 1 Yes → Specify: _____	0 No 1 Yes → Specify: _____	0 No 1 Yes → Specify: _____

Death

1 Date of death: __ __ / __ __ __ / 200 __ (day / month / year)

2 In hospital at time of death? ..... 0 No 1 Yes

3 Sudden death? ..... 0 No 1 Yes

4 During acute heart failure? ..... 0 No 1 Yes

5 During acute ischemia? ..... 0 No 1 Yes

6 Associated with arrhythmia? ..... 0 No 1 Yes

7 Other cardiac? ..... 0 No 1 Yes → Specify: _____

8 Non-cardiac? ..... 0 No 1 Yes → Specify: _____

Echocardiographic Evaluation

Patient Number: __ __ – __ __ __ Patient's Initials: __ __ __

Echocardiographic Evaluation

Date of echocardiogram	__ __ / __ __ __ /200 __ (day / month / year)
1 Heart rate	__ __ __ bpm

Dimensions and LV Function	Value
2 Left ventricular size systole	_____ mm
3 Left ventricular size diastole	_____ mm
4 Ejection fraction	_____ %
5 Intra ventricular septum *(diastole)*	_____ mm
6 Posterior wall *(diastole)*	_____ mm

Diastolic Function	Value
7 Left atrial size, antero-posterior	_____ mm
8 Left atrial size, planimetry	_____ mm^2
9 Mitral E-wave	_____ mm/sec
10 E-wave deceleration time	_____ msec
11 Mitral A-wave	_____ mm/sec
12 Mitral A-wave *(duration)*	_____ msec

Valvular	Severity	Rheumatic?
13 Aortic stenosis	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
14 Aortic regurgitation	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
15 Mitral stenosis	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
16 Mitral regurgitation	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
17 Tricuspid regurgitation	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
19 Other	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
Pericardial Effusion	**Severity**	**Tuberculosis?**
20 Pericardial effusion	0 None 1 Mild 2 Moderate 3 Severe	0 No 1 Yes NA
21 Other conditions	0 No 1 Yes → If Yes: Specify:	
22 Other conditions	0 No 1 Yes → If Yes: Specify:	

Diagnosis

Patient Number: __ __ – __ __ __ Patient's Initials: __ __ __

Diagnosis

Type of Heart Failure *(HF) (please answer all questions)*:

1	Diastolic dysfunction	0 No	1 Yes
2	Systolic dysfunction	0 No	1 Yes
3	Dilated—idiopathic cardiomyopathy *(CM)*	0 No	1 Yes
4	Peripartum cardiomyopathy	0 No	1 Yes
5	Ischemic heart disease	0 No	1 Yes
6	HIV cardiomyopathy	0 No	1 Yes
7	Rheumatic heart disease	0 No	1 Yes
8	Hypertensive cardiomyopathy *(HTN CM)*	0 No	1 Yes
9	Endomyocardial fibroelastosis	0 No	1 Yes
10	Pericardial effusion/tamponade	0 No	1 Yes
11	Other factors	0 No	1 Yes → If Yes: Specify: _____
12	Other factors	0 No	1 Yes → If Yes: Specify: _____

THESUS-HF

Contact Information Log

Patient Number	Full Name	Phone Number	Address	ID Number

Retain at Site

List of contributors to the PAPUCO study

Names	Affiliations
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Data management committee	
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PAPUCO : CASE REPORT FORM

Pan African Pulmonary Hypertension Cohort Study

www.papuco.org

A research collaboration for Africa

CASE REPORT FORM
Baseline
(On database: Master record)

Patient initials

1. ELIGIBILITY CRITERIA

Clinical and echocardiography criteria for the diagnosis of pulmonary hypertension Does the patient has clinical and echoc ardiography evidence of pulmonary arterial hypertension (RVSP>=35 mmHg)	Yes
Patient fulfilling inclusion criteria Does the patient fulfil inclusion criteria (new diagnosis and previously not treated pulmonary hypertension, age>=18 except otherwise approved by ethics committee)?	Yes
Patient able or likely to return for 6-month follow-up	Yes
Patient consented in writing to participate in study	Yes
Date of informed consent/enrolment Enter the date when the patient or next of kin consented to the PAPUCO study.	

2. PATIENT INFORMATION

Folder number Enter the patient hospital or clinic folder number.	
ID or Passport number	
Patient surname	
Patient first name	
Sex	Female Male
Date of birth:	
Country of birth	
Language Enter the language of the patient's mother tongue. (single answer)	Afrikaans Arabic English French Hausa Igbo Ndebele Shona Swahili Xhosa Yoruba
Race Enter the patient's race. (single answer)	African or black Coloured or mixed race Indian or Asian Arab Caucasian or white Other

Education level completed Enter the highest education the patient completed. (single answer).	Never in school Primary Secondary College University
Occupation type Enter the patient's current occupation type. (single answer) Specify the occupation (nurse, farmer, etc) and government grant. _____	Unemployed Student Employed casual Employed part time Employed full time Self employed Homemaker or housewife Government grants or pension Other
Income Enter the self-reported months income of the patient (monthly per capita income). If no personal income, specify income of household breadwinner. (single answer)	Below 30 USD 30 to 99 USD 100 to 299 USD 300 to 499 USD 500 to 999 USD 1000 to 1999 USD 2000 to 4999 USD more than 5000 USD
Type of accommodation Enter the type of accommodation the patient lives in. (single answer)	House or permanent building Shack on serviced site with sanitation Shack without sanitation Traditional housing or hut Other
Referral source Enter the referral source the patient was referred from. (single answer)	Other Hospital Community clinic General practitioner Medical ward of this hospital Outpatient department of this hospital Other
Research sample ID Enter the patient research sample ID that will be written on the laboratory tubes. Enter your own sample ID number or if the field is left blank, a sample ID will be generated for the patient research sample. Please label all samples using	
Patient mobile phone number	
Other (partner, friend, parents) phone number 1	
Other phone number 2	

3. LOCATION

Street Address	
City/Town	
Post Code	
Country	

4. MEDICAL HISTORY

Family history of CVD Does the patient have a positive family history of cardiovascular diseases (Example: high blood pressure, heart attack, chest pain/angina)	YES NO
Hypercholesterolemia Has the patient been diagnosed with high cholesterol?	YES NO

Hypertension Has the patient been diagnosed with hypertension?	YES NO
Diabetes Has the patient been diagnosed with diabetes?	YES NO
Beta-thalassemia Has the patient been diagnosed with beta-thalassemia?	YES NO
Sickle-cell anaemia Has the patient been diagnosed with sickle cell anaemia?	YES NO
Rheumatic disease Has the patient been diagnosed with rheumatic disease (E.g. Rheum atoid arthritis)?	YES NO
Type of rheumatic disease Select the type of rheumatic disease. (multiple answers)	Scleroderma (systemic sclerosis) Mixed connective tissue disease (MCTD) Systemic lupus erythematosus (SLE) Rheum atoid arthritis (RA) Systemic necrotizing vasculitis Idiopathic inflamm atory myositis Other
Deep vein thrombosis: Has the patient been diagnosed with deep vein thrombosis (DVT)?	YES NO
Pulmonary embolism: Has the patient been diagnosed with pulm onary em bolism (PE)?	YES NO
Chronic lung disease Has the patient been diagnosed with chronic lung disease?	YES NO
Type of chronic lung disease Select the type of chronic lung disease. COPD includes pulmonary emphysema. Destructive lung disease in HIV due to TB, PCP or other pulmonary infection should be classified bronchiectasis. (multiple answers)	Asthma COPD / emphysema Bronchiectasis Lung cancer Other
Specify chronic lung disease Specify the chronic lung disease of the patient. Please be specific.	
Chronic liver disease Has the patient been diagnosed with chronic liver disease?	YES NO
Type of chronic liver disease Select the type of chronic liver disease. (multiple answers)	Hepatitis B Hepatitis C Metabolic-toxic Schistosomiasis liver disease Other

5. ENVIRONMENT

Living at high altitude Does or did the patient live at high altitude (>1500 meter above sea level)?	YES NO
Years at high altitude	
Working in mine Does or did the patient work in a mine?	YES NO
Indoor cooking or heating without chimney Does or did the patient cook indoor using burnable (e.g. wood, charcoal, kerosene, paraffin, dung etc.) without chimney?	YES NO
Smoking habit Does or did the patient smoke? (single answer)	Current smoker Ex-smoker Never smoked
Number of pack-years	
Date of discontinuation: Enterthe date the patient stopped smoking	
Alcohol abuse Does or did the patient abuse alcohol?	YES NO
Recreational drug use Does or did the patient take drugs?	YES NO

Type of recreational drug use Select the type of recreational drug use. (multiple answers)	Marihuana Amphetamines Crack Cocaine Heroin Other

6. INFECTIOUS DISEASES

Previous TB Has the patient ever been diagnosed or treated for TB?	YES NO
How many TB episodes: How many times was the patient diagnosed for TB in his life?	
Date of last episode: Enter the date of the latest TB episode.	Format: YYYY-MM-DD
Site of TB Select the site of infection of the latest TB episode (single answer)	Pulmonary and/or pleural TB Abdominal TB Lymph node TB CNS TB Pericardial TB Disseminated TB Other site of TB
Treated for TB Has the patient received TB treatment for his/her latest TB episode?	YES NO
Completed TB treatment Has the patient completed treatment for his/her latest TB episode? Select 'Yes' if TB treatment was completed; select 'No' if TB treatment was not completed or if patient is still on TB treatment.	YES NO
Concurrent TB treatment Is the patient still on TB treatment?	YES NO

HIV testing Has the patient been tested for HIV? If not, council and test the patient for HIV according to your national HIV testing guidelines. If patient refuses to get tested select 'No'.	YES NO
HIV Status Enter the HIV status of the patient.	Positive Negative
Date of HIV diagnosis Enter the date of HIV testing. If the exact date is unknown, calculated the approximate date according to patient information.	
CD4 nadir CD4 nadir is the lowest CD4 count of the patient ever measured. If it is identical with the field 'Latest CD4 count', fill in both fields with the same CD4 count.	cells per 10^6/L
Latest CD4 count Enter the latest CD4 count of the patient.	cells per 10^6/L
Date of latest CD4 count Enter the date of the latest CD4 count.	
Latest HIV viral load Enter the latest HIV viral load in plasma. If HIV viral load is suppressed in plasma according to the lowest level of detection of your laboratory enter '0'.	copies/mol
Date of latest viral load Enter the date of the latest HIV viral load in plasma.	
Antiretroviral therapy Is the patient currently receiving ART?	YES NO
Date of ART initiation Enter the date when patient was started on ART.	

ART regimen Choose from the ART regimen of the patient. (single answer)	TDF3TCEFV TDF3TCNVP TD3TCLPVr AZT3TCEFV AZT3TCNVP AZT3TCLPVr D4T3TCEFV DVT3CNVP D4T3CLPVr PMTCT regimen Other

Exposure to schistosomiasis Has the patient ever lived or does he/she live in an endemic region for schistosomiasis?	YES NO
Years of exposure Enter the years (cumulative years) of exposure to an endemic region for schistosomiasis.	years
Haematuria at presentation: Does or did the patient experience haematuria?	YES NO
Microscopy for schistosomiasis: Was microscopy performed to diagnose schistosomiasis?	YES NO
Specimen for microscopy Enter the type of specimen that was used to diagnose schistosomiasis. (single answer)	Faeces Urine Rectal biopsy Bladder biopsy
Schist soma eggs present Select the type of schistosoma that was identified. (single answer)	S.mansoni S.haemotobium S.intercalatum S.guineensis
Abdominal ultrasound **Was abdominal ultrasound performed to screen for schistosomiasis.**	YES NO
Ultrasound findings suggestive for schistosomiasis Select ultrasonographic findings that are highly suggestive of schistosomiasis. (single answers)	Normal abdominal ultrasound Liver left lobe enlargement Periportal fibrosis Liver left lobe enlargement AND Periportal fibrosis Thickening or calcification of bladder wall Hydronephrosis Thickening or calcification of bladder wall AND Hydronephrosis Other abdominal pathology
Previous treatment for schistosomiasis Did the patient ever receive treatment for schistosomiasis? Example: single oral dose of the drug praziquantel.	YES NO

Specify treatment:

_____

(On database: Baseline visit data)

1. PATIENT INFORMATION Date

of visit Enter the date of patient visit (=date of clinical assessment).	Format: YYYY-MM-DD

2. CLINICAL PRESENTATION

Shortness of breath Does the patient suffer shortness of breath?	YES NO
Bluish lips or skin Does the patient experience bluish lips or skin?	YES NO
Non-productive cough Does the patient suffer non-productive couch?	YES NO
Fatigue Does the patient suffer fatigue?	YES NO
Dizziness Does the patient suffer dizziness?	YES NO
Syncope Does the patient suffer episodes of syncope or near syncope?	YES NO
Palpitations Does the patient experience palpitations?	YES NO
Angina Does the patient suffer chest pain (angina pectoris)?	YES NO
NYHA classification Please read below and select carefully. (single answer)	NYHA I NYHA II NYHA III NYHA IV

NYHA I: No symptoms and no limitation in ordinary physical activity.
NYHA II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
NYHA III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
NYHA IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

3. CLINICAL INVESTIGATIONS

Karnofsky Scale

The Karnofsky Performance Scale is an assessment tool used to assist clinicians and caretakers in measuring a patient's ability to carry out activities of daily living. Read carefully and circle the appropriate number.

Able to carry on normal activity and to work; no special care needed.	**100**	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Body weight Enter the weight of the patient	kg
Body height Enter the height of the patient	cm
Systolic blood pressure at rest Enter the SYSTOLIC value of patient blood pressure	mmHG
Diastolic blood pressure at rest Enter the DIASTOLIC value of patient blood pressure	mmHG
Pulse at rest Enter patient pulse at rest.	bpm
Pulse oxymetry at rest Enter patient pulse oxymetry reading at rest (SpO2).	%
Respiration rate at rest Enter patient respiration rate at rest.	breaths per minute
JVP raised Is jugular venous pressure (JVP) raised?	YES NO
Peripheral oedema Does the patient have clinical oedema?	YES NO
Heart auscultation: Select findings from patient heart auscultation. (multiple answers)	Normal Loud P2 heart sound Right-sided S3 gallop Systolic murmur Diastolic murmur Other murmur
ECG performed Did the patient under go ECG studies at rest? Of note: An ECG should be performed at baseline and 6-month follow-up.	YES NO
Date of ECG Enter the date of ECG.	Format: YYYY-MM-DD
ECG heart rhythm Select ECG rhythm of the patient. (multiple answers)	Normal sinus rhythm AV Block I AV Block II Wenckebach AV Block II Mobitz AV Block III AV Dissociation Wolff Parkinson White Preexcitation Atrial fibrillation Atrial flutter Paroxysmal supr aventricular tachycardia AV Re-entry tachycardia Sinus tachycardia P Culminate Right ventricular hypertrophy Left ventricular hypertrophy
Chest X-ray performed Was a chest X-ray performed? Of note: A chest X-ray should be performed at baseline visit.	YES NO
Date of Chest X-ray Enter the date of Chest X-ray.	Format: YYYY-MM-DD
Chest X-ray findings Select chest X-ray findings. (single answer)	Normal cardio thoracic ratio Suggestive for left heart enlargement Suggestive for right heart enlargement Prominence of pulmonary arteries

- Suggestive for right heart enlargement and prominence of pulmonary arteries
- Suggestive for combined heart enlargement
- Suggestive for combined heart enlargement and prominence of pulmonary arteries
- Primary lung disease

4. SIX-MINUTE WALK TEST

Baseline heart rate	bpm
Baseline pulse oxymetry	%
Baseline dyspnoea (single answer)	0 Nothing at all 0.5 Very very slight 1 very slight 2 Slight (light) 3 Moderate 4 Somewhat severe 5 Severe 6 7 Very severe 8 9
Baseline fatigue (single answer)	0 Nothing at all 0.5 Very very slight 1 very slight 2 Slight (light) 3 Moderate 4 Somewhat severe 5 Severe 6 7 Very severe 8 9
Distance walk in 6 minutes Enterthe total distance the patient walked in 6 minutes.	meters
Postwalk heart rate	bpm
Postwalk pulse oxymetry	%
Postwalk dyspnoea (single answer)	0 Nothing at all 0.5 Very very slight 1 very slight 2 Slight (light) 3 Moderate 4 Somewhat severe 5 Severe 6 7 Very severe 8 9
Postwalk fatigue (single answer)	0 Nothing at all 0.5 Very very slight 1 very slight 2 Slight (light) 3 Moderate 4 Somewhat severe 5 Severe 6 7 Very severe 8 9

5. LABORATORY

White cell count	x 10^9/L
Red cell count	x 10^9/L
Haemoglobin	g/dL
Haematocrit	%
Platelets	x 10^9/L
Eosinophil count	%
Sodium	mmol/L
Potassium	mmol/L
Urea	mmol/L
Creatinine	µmol/L
Bilirubin total	µmol/L
AP	U/L
GGT	U/L
ALT	U/L
AST	U/L
Cholesterol	mmol/L
Triglycerides	mmol/L
HDL Cholesterol	mmol/L
LDL Cholesterol	mmol/L
Glucose	mmol/L
CRP	mg/L
ESR	millimetres per hour
TSH	mix/L
T4	pmol/L
Arterial blood gases pH	pH
Arterial blood gases PO2	mmHg
NT Pro BNP	mmol/L
HBsAG	N/A Positive Negative
Anti-HCV Screening for Hepatitis C.	N/A Positive Negative
ANA The presence of Antinuclear Antibody (ANA) is indicative of lupus erythematosus, mixed connective tissue disorder, and many other autoimmune diseases.	N/A Positive Negative
anti-ENA Anti-extractable nuclear antigen (anti-ENA) is a grouping of antibodies often used to screen for mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), and Sjögren's and commonly is composed of four tests: anti-Sm (for SLE), anti-RNP (for MCTD), anti-La and anti-Ro (for Sjögren's).	N/A Positive Negative
anti-dsDNA Anti-double stranded DNA (dsDNA) antibodies are linked to SLE.	N/A Positive Negative
Other laboratory results Enter any other relevant laboratory result. Example: bet a thalasemia, sickle-cell anaemia, RPR/TPHA for syphilis, etc.). Use scientific abbreviations, display unit, and normal range	

6. ECHOCARDIOGRAPHY

Echocardiographic assessment Is an echocardiographic examination performed at this visit?	YES NO
Date of Echocardiography Enter the date of echocardiographic examination	
Heart rate:	beats per minute
Aortic root size	mm
Left atrial size	mm
Intraventricular septum diastolic diameter (IVSD)	mm
Intraventricular septum systolic diameter (IVSS)	mm
Left ventricular end diastolic diameter (LVEDD)	mm
Left ventricular end systolic diameter (LVESD)	mm
Posterior wall diastolic diameter (PWD)	mm
Posterior wall systolic diameter (PWS)	mm
Fractional shortening (FS)	%
Ejection fraction calculated (EF1)	%
Ejection fraction visual estimations (EF2)	%
Regional wall motion abnormality (RWMA)	YES NO
Regional wall motion abnormality type (RWMA type) (single answer)	Anterior Inferior Lateral
Diastolic function assessment Are diastolic function tests performed?	YES NO
Mitral E-wave	m per second
Mitral A-wave	m per second
Deceleration time	msec
Right atrial size (single answer)	Normal Mildly enlarged Moderately enlarged Severely enlarged
Right ventricle size (single answer)	Normal Mildly enlarged Moderately enlarged Severely enlarged
Right Ventricular Systolic Pressure (RVSP)	mmHg
TAPSE (Tricuspid annular plane systolic excursion)	mm
Aortic stenosis (single answer)	No Mild Moderate Severe
Aortic stenosis mean gradient	mmHg
Mitral stenosis (single answer)	No Mild Moderate Severe
Mitral stenosis mean gradient	mmHg
Mitral stenosis valve area (doppler)	cm
Aortic regurgitation (single answer)	No or traces Mild Moderate Severe
Mitral regurgitation (single answer)	No or traces Mild Moderate Severe
Tricuspidal regurgitation (single answer)	No or traces Mild Moderate Severe

Valve repair	YES NO
Repaired valve(s) Select the repaired valve(s). (multiple answers)	Mitral valve Aortic valve Tricuspid valve Pulmonary valve
Reason for valve repair Enter the clinical reason for valve repair. (Example: rheumatic fever, congenital heart disease, etc.)	
Valve replacement	YES NO
Replaced valve(s) Select the replaced valve(s). (multiple answers)	Mitral valve Aortic valve Tricuspid valve Pulmonary valve
Reason for valve replacement Enter the clinical reason for valve replacement. (Example: rheumatic fever, congenital heart disease, etc.)	
ECHO diagnosis Enter the diagnosis of echocardiographic examination. The diagnosis MUST be PULMONARY HYPERTENSION. Also describe all other pathological finding.	

7. RIGHT HEART CATHETERIZATION

Right heart catheterisation Did the patient under go right heart catheterisation?	YES NO
Date of right heart catheterisation Enter the date of right heart catheterisation.	
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
Mean right atrial pressure	mmHg
Right ventricular systolic pressure	mmHg
Right ventricular diastolic pressure	mmHg
Pulmonary artery wedge pressure	mmHg
Pulmonary artery systolic pressure	mmHg
Pulmonary artery diastolic pressure	mmHg
Mean pulmonary artery pressure	mmHg
Cardiac output (CO)	litre/min
Cardiac index	liter/min/sqm
Systemic vascular resistance	Woods units
Pulmonary vascular resistance	Woods units
Right heart catheterization diagnosis Enter the diagnosis of right heart catheterisation. The diagnosis MUST be PULMONARY HYPERTENSION. Also describe all other pathological finding.	

8. **DIAGNOSIS**

Investigation used to make final diagnosis Select the investigations used to make final diagnosis.	ECHO only ECHO **and** cardiac catheterization
Date of final diagnosis Enter the date of final diagnosis.	
Final diagnosis Select the final diagnosis. (single answer)	Pulmonary Arterial Hypertension (PAH) Pulmonary Veno Occlusive Disease and/or Pulmonary Capillary Haem angiomatosis PAH due to Left Heart Disease PAH due to Lung Disease and/or Hypoxia Chronic Thromboembolic PAH PAH due to unclear/multifactorial mechanism
Aetiology of PAH (single answer)	Idiopathic PAH Heritable (BMPR2, ALK-1, endoglin, unknown) Drugs and toxins induced Associated with Connective Tissue Disease (scleroderma) Associated with Connective Tissue Disease (not scleroderma) Associated with HIV infection Associated with Portal Hypertension Associated with Congenital Heart Disease Associated with Schistosomiasis Associated with Chronic Haemolytic Anaemia (including sickel cell anaemia, thalassemia)
Aetiology of PAH due to Left Heart Disease (single answer)	Left Ventricular Systolic Dysfunction Left Ventricular Diastolic Dysfunction Valvular disease
Aetiology of PAH due to Lung Disease and/or Hypoxia (single answer)	Chronic obstructive pulmonary disease Interstitial lung disease Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental abnormalities
Aetiology of PAH due to unclear/multifactorial mechanisms (single answer)	Haematological disorders - Myeloproliferative disorders Haematological disorders - Splenectomy Systemic disorders - Sarcoidosis Systemic disorders - Pulmonary Langerhans cell histiocytosis Systemic disorders - Lymphangioleiomyomatosis Systemic disorders - Neurofibromatosis Systemic disorders - Vasculitis Metabolic disorders - Glycogen storage disease Metabolic disorders - Gaucher's disease Metabolic disorders - Thyroid disorders Other - Tumour obstruction Other - Fibrosing mediastinitis
Causality classification The causality classification rates the degree of certainty of your choice (single answer)	Certain Probable/likely Possible Unclassifiable
Substantiate the final diagnosis and notes on the case Justify your choice in the text box and provide details of additional examinations the patient under went for the final diagnosis. Elaborate also on your assumptions and causality classification. Please describe causality and temporal relationship.	

9. TREATMENT

Disease-targeted drug therapy Disease-targeted drug therapy are therapeutics that are licensed for the treatment of pulmonary hypertension. Please fill out this section at BASELINE and 6-MONTH FOLLOW-UP	
Start date of diseases-targeted drug therapy Enter the date of final diagnosis.	
Disease-targeted drug therapy Select the disease targeted drug therapy for PAH. Example: Sildenafil is a Phosphodiesterase 5 inhibitor (multiple answers)	Endothelin receptor antagonist Phosphodiesterase 5 inhibitor Prostaglandins High dose calcium channel blocker Clinical trial therapy
Heart failure drug therapy This section captures information on heart failure drug therapy. The information is a snapshot of the treatment that the patient receives at this visit including the drugs that the patient is prescribed at this visit. Please fill out this section at BASELINE and 6- MONTH FOLLOW-UP. **(in daily dose)**	
Furosemide	mg
Hydrochlorothiazide	mg
Spironolactone	mg
Captopril	mg
Enalapril	mg
Perindopril	mg
Ramipril	mg
Atenolol	mg
Bisoprolol	mg
Carvedilol	mg
Metoprolol	mg
Amlodipine	mg
Nifedipine	mg
Digoxin	µg
Anticoagulants Does the patient receive anticoagulants? (Example: warfarin	YES NO
Oxygen Does the patient receive long-term home oxygen?	YES NO
Other heart failure treatment Drug 1	
Other heart failure treatment Drug 2	
Other heart failure treatment Drug 3	

Antiretroviral therapy This section applies ONLY to patients that are HIV positive and not yet on antiretroviral therapy (ART) and are started on ART during the study period.	
ART-naive patients: Initiation of ART Is the patient initiated on ART during the study period?	YES NO
Start date of ART Enter the start date ART initiation	
Initiated ART regimen Select the initiated ART regimen. (single answer)	TDF 3TC EFV TDF 3TC NVP TDF 3TC LPVr AZT 3TC EFV AZT 3TC NVP AZT 3TC LPVr D4T 3TC EFV D4T 3TC NVP D4T 3TC LPVr Other

Anthelmintic drug therapy This section applies ONLY to patients that are diagnosed with pulmonary hypertension associated with schistosomiasis.	
Treatment with anthelmintic drug Is the patient treated with an anthelmintic drug during the study period?	YES NO
Start date of anthelmintic drug Enter the start date of the anthelmintic drug. Example: Praziquantel	
Specify anthelmintic drug therapy Specify the anthelmintic drug therapy the patient received at baseline. (drug name, drug class, daily dose, duration)	

10. Additional notes of the case

Summaries the case in writing and comment on specific findings

ATTENTION
Upload ECG and Chest X ray Store ECHO on your ECHO machine and backup the data.

PAPUCO – Pan African Pulmonary Hypertension Cohort Study

6-Month Follow-Up Questionnaire

Note: Allowable window for 6-month follow-up clinic visit is 5 to 9 months from baseline.
In addition, a verbal autopsy should be performed to investigate whether patient is alive on 31 December 2013.

Patient number (e.g. FT19750102M)	

Patient lost to follow-up? ☐ YES ☐ NO	**Reason for lost to follow-up** ☐ No telephone contact or unreachable (>15 attempts on 3 different days) ☐ Lack of transportation access to the clinic ☐ Financial difficulties to pay for transport or clinic visit costs ☐ Withdraw of informed consent ☐ Other _____

☐ **6-Month follow-up only through phone contact only**

Date of visit/phone call: Format: DD-MMM-YYYY

1. Clinical assessment at 6 months ☐ NOT DONE

Shortness of breath	☐ YES	☐ NO	**Fatigue**	☐ YES	☐ NO	**Palpitations**	☐ YES	☐ NO
Bluish lips or skin	☐ YES	☐ NO	**Dizziness**	☐ YES	☐ NO	**Angina**	☐ YES	☐ NO
Cough	☐ YES	☐ NO	**Syncope**	☐ YES	☐ NO	**Karnofsky Score**	_____ (between 0 and 100)	
WHO functional class	☐ WHO FC I ☐ WHO FC II ☐ WHO FC III ☐ WHO FC IV		**Pulse** _____ bpm			**Blood pressure** _____/_____ mmHg		

2. Six minutes walk test at 6 months ☐ NOT DONE

Baseline heart rate	**Baseline SpO2**	**Distance walked in 6 minutes**	**Post walk heart rate**	**Post walk SpO2**
_____ bpm	_____ %	_____ meters	_____ bpm	_____ %

Baseline dyspnoea	**Baseline fatigue**
☐ 0 Nothing at all	☐ 0 Nothing at all
☐ 0.5 Very very slight	☐ 0.5 Very very slight
☐ 1 very slight	☐ 1 very slight
☐ 2 Slight (light)	☐ 2 Slight (light)
☐ 3 Moderate	☐ 3 Moderate
☐ 4 Somewhat severe	☐ 4 Somewhat severe
☐ 5 Severe	☐ 5 Severe
☐ 6	☐ 6
☐ 7 Very severe	☐ 7 Very severe
☐ 8	☐ 8
☐ 9	☐ 9
☐ 10 Very very severe	☐ 10 Very very severe

Post walk dyspnoea	**Post walk fatigue**
☐ 0 Nothing at all	☐ 0 Nothing at all
☐ 0.5 Very very slight	☐ 0.5 Very very slight
☐ 1 very slight	☐ 1 very slight
☐ 2 Slight (light)	☐ 2 Slight (light)
☐ 3 Moderate	☐ 3 Moderate
☐ 4 Somewhat severe	☐ 4 Somewhat severe
☐ 5 Severe	☐ 5 Severe
☐ 6	☐ 6
☐ 7 Very severe	☐ 7 Very severe
☐ 8	☐ 8
☐ 9	☐ 9
☐ 10 Very very severe	☐ 10 Very very severe

3. Echocardiography at 6 months ☐ NOT DONE

LV-EF calculated _____ %	**LV-EF visual** _____ %	**RVSP** _____ mmHg	**TAPSE** _____ mm
Right atrial size	☐ Normal ☐ Mildly enlarged ☐ Moderately enlarged ☐ Severely enlarged	**Right ventricle size**	☐ Normal ☐ Mildly enlarged ☐ Moderately enlarged ☐ Severely enlarged

4. Hospitalisation ☐ N/A **and death** ☐ N/A **at 6 months**

Hospitalization within 6 months of follow-up? ☐ YES ☐ NO	**Total number of days in hospital** _____ days
Reason for admittance:	
Alive at 6-month follow-up? ☐ YES ☐ NO	**Date of death:** Format: DD-MMM-YYYY
Cause of death:	

5. Verbal autopsy 31 December 2013 ☐ NOT DONE

Alive on 31 December 2013 ☐ YES ☐ NO ☐ No telephone contact or unreachable (>15 attempts on 3 different days)	
Date of death: Format: DD-MMM-YYYY	**Cause of death:**

_____
Initial and date of person completing the form

Note: Allowable window for 6-month follow-up clinic visit is 5 to 9 months from baseline.
In addition, a verbal autopsy should be performed to investigate whether patient is alive on 31 December 2013.

Definitions:

WHO functional class

WHO FC I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea of fatigue, chest pain or near syncope.
WHO FC II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
WHO FC III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
WHO FC IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Karnofsky Performance Score

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

_____
Initial and date of person completing the form

COMITE NATIONAL D'ETHIQUE DE LA RECHERCHE POUR LA SANTE HUMAINE

Arrêté N° 0977/A/MINSANTE/SESP/SG/DROS/ du 18 avril 2012 portant création, organisation et fonctionnement des comités d'éthique de la recherche pour la santé humaine au sein des structures relevant du Ministère en charge de la santé publique

N° 2013/11/363/L/CNERSH/SP Yaoundé, le 21 Novembre 2013

Cnethique_minsante@yahoo.fr

CLAIRANCE ETHIQUE

Le Comité National d'Ethique de la Recherche pour la Santé Humaine (CNERSH), en sa session du 21 novembre 2013, a examiné le dossier de demande de clairance éthique pour le projet de recherche intitulé **«Pulmonary hypertension in patients referred to specialized cardiovascular centers in Douala and Shisong, Cameroon»** soumis par le Docteur **DZUDIE TAMDJA Anastase**, Investigateur principal, Hôpital Général de Douala.

Le projet est d'un grand intérêt scientifique et social. La procédure de l'étude est bien documentée et claire. Les risques liés à l'étude sont présentés et seront minimisés par un personnel compétent. La notice d'information et le formulaire de consentement éclairé, en français et en anglais, sont bien élaborés et simples à comprendre. Les mesures prises pour garantir la confidentialité des données collectées sont incluses dans le document. Les CVs des Investigateurs les décrivent comme des personnes compétentes, capables de mener à bien cette étude. Pour toutes ces raisons, le Comité National d'Ethique approuve pour une durée de deux ans, la mise en œuvre de la présente version du protocole.

Les investigateurs sont responsables du respect scrupuleux du protocole approuvé et ne devraient y apporter aucun amendement aussi mineur soit-il, sans avis favorable du CNERSH. Les investigateurs sont appelés à collaborer pour toute descente du CNERSH pour le suivi de la mise en œuvre du protocole approuvé. Le rapport final du projet devra être soumis au CNERSH et aux autorités sanitaires du Cameroun.

La présente clairance peut être retirée en cas de non respect de la réglementation en vigueur et des recommandations sus-mentionnées.

En foi de quoi, la présente clairance éthique est délivrée pour servir et valoir ce que de droit.

Ampliations

- MINSANTE

Le Président

Pr Lazare KAPTUE

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • **Facsimile** [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

15 June 2011

HREC REF: 241/2011

Prof K Sliwa
Hatter Institute
Cape heart Centre
4th Floor, Chris Barnard Building

Dear Prof Sliwa

PROJECT TITLE: THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) REGISTRY

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

Thank you for your response to the queries raised.

It is a pleasure to inform you that the FHS HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until 28 June 2012.

Please send us an annual progress report (website form FHS 016) if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

lemjedi

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

lemjedi

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Annual Progress Report

Date	27 November 2013
HREC REF Number	241/2011
Protocol number (if applicable) & Protocol title	The Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry
Principal Investigator	Prof. Karen Sliwa
Department / Office Internal Mail Address	Hatter Institute for Cardiovascular Research in Africa

List of documentation

The information collected via the registry has not changed. No additional approval is indicated.

We have presented preliminary findings of the registry at:

1. **World Congress of Paediatric Cardiology, Cape Town, February 2013**
2. **Pan African Society of Cardiology meeting, Dakar, Senegal, May 2013**
3. **NRF Mozambique-South Africa meeting, Maputo 20th November 2013 (slides attached).**
4. **The data will be presented at the World Congress of Cardiology, Melbourne, Australia, May 2014.**

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	This serves as notification of annual approval, including all documentation described above.		
☐ Not approved	See attached comments.		
Type of review	☒ Expedited	☐ Full committee	
Expiry date	2014		
Signature Chairperson of the HREC		Date	28/11/13

UNIVERSITY OF UYO TEACHING HOSPITAL

P. M. B. 1136, UYO, AKWA IBOM STATE

Professor Etete J. Peters FWACP, JP
Chief Medical Director
08037039374 08052368852

Dr. Emem A. Bassey FWACP, FICS, FCAI
Chairman, Medical Advisory Committee
08033486981

Mrs. Edak U. Umondak BA(Hons), MLS
Director of Administration
08023502144

Our Ref: UUTH/AD/S/96/VOL.VII/496

Your Ref: .....

14th September, 2011

Date: .....

UNIVERSITY OF UYO TEACHING HOSPITAL, UYO
HEALTH REVIEW COMMITTEE.

APPROVAL CERTIFICATE

Principal Investigator: **Dr. Patience A Udo**
Protocol Title: "The Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry"

STATUS

The University of Uyo Teaching Hospital, Uyo Institutional Review Committee has reviewed your protocol titled "The Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry".

The research Protocol described above has been reviewed by the University of Uyo Teaching Hospital, HRC and approval given as indicated.

J. E. Inyang
Secretary, UUTH,
Uyo HRC

e-mail: info@uuthuyo.com uuthuyo@gmail.com

AMINU KANO TEACHING HOSPITAL

P. M. B. 3452, ZARIA ROAD, KANO. (☎: 07068297399, 08057203511, 064 - 377085 - 8)
www.akth.org, E-mail: enquiries@akth.org, email: (akthkano@yahoo.com)

Chairman Board of Management	Ag. Chief Medical Director	Chairman M. A. C.	Director of Administration
PROF. IDRIS MUHAMMAD NNOM, OON, FAS, MD, FRCP	DR. HADIZA S. GALADANCI FWACS, FICS, MRCOG	DR. HADIZA S. GALADANCI FWACS, FICS, MRCOG	ALH. MUHD. SULAIMAN, AHAN B. Ed, CHPM

NHREC/21/08/2008/AKTH/EC/850

AKTH/MAC/SUB/12[A]/P3/IV/950

2nd November, 2011

Dr Mahmud Umar Sani
Department of Internal Medicine
AKTH, Kano

ufs:

The Head of Department,
Department of Internal Medicine
AKTH, Kano

RE: ETHICAL APPROVAL

PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) REGISTRY

Further to your response in respect of the above research proposal, the Committee has considered your proposal and noted same as a prospective study.

In view of this, Ethical approval is hereby granted to conduct the research.

However, the approval is subject to periodic reporting of the progress of the study and its completion to the Ethical Committee.

Best regards.

BARA'ATU KABIR (Mrs)
SECRETARY
FOR: CHAIRMAN, ETHICAL COMMITTEE

FEDERAL MEDICAL CENTRE

(QUEEN ELIZABETH HOSPITAL)

P.M.B. 7001, UMUAHIA, ABIA STATE, NIGERIA
Tel: 088-220025,220981-2,www.Fmcumuahia.org
email: fmcumuahia@fmcumuahia.org

Chairman, Management Board
Dr. Abali Chuku, MBBS; FWACS; FICS; Dip HSM; Cert HRM
Medical Director/Chief Executive.
O. Chijioke, MBA; MPA; ACIS AHAN; FCAI; FInstAM.JP
Head of Administration/Secretary to the Board.

Dr. Uche Nwamoh MD, FWACP, FMCPH
Chairman, Medical Advisory Committee

HEALTH RESEARCH ETHICS COMMITTEE (HREC)

7th February, 2013

Notice of Full Approval after full Committee Review

Protocol's full title including official abbreviations:
The Pan African Pulmonary Hypertension Cohort (PAPUCO)

Health Research Committee assigned number: FMC/QEH/G.596/Vol.8/036

Name of Principal Investigator: Dr. Okechukwu S. Ogah

Address of Principal Investigator: Dept. of Medicine
FMC, Umuahia

Date of receipt of valid application: 20th August, 2012

Date of meeting when final determination of research was made: 13th December, 2012

This is to inform you that the research described in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and given full approval by the Health Research Ethics Committee.

This approval dates from 1st February, 2013 to 1st July, 2013 If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these date. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavour to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserved the right to conduct compliance visit to your research site without previous notification.

You are please required to donate a copy of this research work to the Health Research Ethics Committee of the Federal Medical Centre, Umuahia.

Thank you.

Dr. I.O. Iwegbu
Chairman, HREC
For: Medical Director

AMINU KANO TEACHING HOSPITAL

P. M. B. 3452, ZARIA ROAD, KANO. (☎: 07068297399, 08057203511, 064 - 377085 - 8)
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NNOM, OON, FAS, MD, FRCP	FWACS, FICS, MRCOG	FWACS, FICS, MRCOG	B. Ed, CHPM

NHREC/21/08/2008/AKTH/EC/850

AKTH/MAC/SUB/12[A]/P3/IV/950

2nd November, 2011

Dr Mahmud Umar Sani
Department of Internal Medicine
AKTH, Kano

ufs:

The Head of Department,
Department of Internal Medicine
AKTH, Kano

RE: ETHICAL APPROVAL

PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) REGISTRY

Further to your response in respect of the above research proposal, the Committee has considered your proposal and noted same as a prospective study.

In view of this, Ethical approval is hereby granted to conduct the research.

However, the approval is subject to periodic reporting of the progress of the study and its completion to the Ethical Committee.

Best regards.

BARA'ATU KABIR (Mrs)
SECRETARY
FOR: CHAIRMAN, ETHICAL COMMITTEE

FEDERAL MEDICAL CENTRE

Bisi Onabanjo Way, Idi-Aba, P. M. B. 3031 (Sapon Post Office), Abeokuta, Nigeria.
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Medical Director
Dr. O. S. Sotiloye
MBBS, FWACS, FICS, Dip. Reproductive Med & Biology (Geneva) D MAS

Chairman Medical Advisory Committee
Dr. A. D. Eni-Olorunda
MB; BS FWACS FMC Opht

Director of Admin. & Sec. Board of Mgt.
Mr. O. A. Oyeku
Bsc, MPA, AMNIM, AIPM, AHAN

Our Ref:_____ Your Ref:_____ Date: 12th December,2011.

NAME OF PRINCIPAL INVESTIGATOR: DR. O. S. OGAH
c/o Dr. (Mrs.) T. Olunuga

TITLE OF STUDY: Implementation of the pan African pulmonary hypertension corhot (PAPUCO) Registry

RESEARCH LOCATION: FEDERAL MEDICAL CENTRE (FMC), ABEOKUTA

PROTOCOL NUMBER: FMCA/238/10/2011

HREC ASSIGNED NUMBER: HREC/10/33/2011

NOTIFICATION OF FULL MEMBERS APPROVAL OF RESEARCH PROTOCOL

This is to inform you that the Federal Medical Centre, Abeokuta Health Research Ethics Committee (HREC) at its sitting on 9th December,2011 decided to give full member approval to your research proposal, after necessary reviews and corrections, under the regulations guiding experiments in human subjects.

This approval is for a period of one year from 12th of December, 2011 to 11th December, 2012. If there is delay in starting this research, please inform the HREC so that dates of approval can be adjusted accordingly. Note that no activity related to this research may be conducted outside these dates. No changes are permitted in the research without prior approval by HREC.

All forms and questionnaires used in this study must carry the HREC assigned number and the duration of HREC approval.

You are to note further that, the National Code of Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations, to follow trends of the code. Please ensure that any adverse effect from your study is promptly reported to the HREC Federal Medical Centre, Abeokuta.

You are expected to submit a progress report to this Committee every three (3) months from the date of approval. The HREC reserves the right to conduct compliance visits on your research sites without previous notification.

Dr. (Mrs.) O. F. Dedeke
For: Chairman Hospital Research Ethics Committee

REPÚBLICA DE MOÇAMBIQUE

MINISTÉRIO DA SAÚDE

COMITÉ NACIONAL DE BIOÉTICA PARA A SAÚDE
IRB00002657

Exm Senhor
Dr. Albertino Damasceno
HCM

Ref: 476/CNBS/12 **Data 20 de Dezembro de 2012**

Assunto: *Autorização para iniciar o* registo de doentes com hipertensão pulmonar *no Hospital Central de Maputo ."*

No dia 20 de Dezembro de 2012, o Comité Nacional de Bioética para a Saúde (CNBS) analisou o pedido para iniciar o registo de doentes com hipertensão pulmonar no Hospital Central de Maputo referentes ao protocolo intitulado: " ***Epidemiologia da hipertensão Pulmonar em Maputo (PAPUCO)"***, sobre o mesmo, o CNBS chegou a seguinte conclusão:

O CNBS não vê nenhum inconveniente de ordem ética que impeça a realização do estudo pelo que, dá a sua devida autorização.

Contudo, recomenda aos investigadores que o mantenham informado do decurso do estudo.

Faz notar que a aprovação ética não substitui a autorização administrativa.

Sem mais de momento, queiram aceitar as nossas cordiais saudações.

Dr. João

ENDEREÇO:
MINISTÉRIO DA SAÚDE
C. POSTAL 264
Av. Eduardo Mondlane/Salvador Allende
MAPUTO – MOCAMBIQUE

Telefones: 430814/427131(4)
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258 (1) 33320